THE 10TH INTERNATIONAL

BREAST DENSITY & CANCER RISK ASSESSMENT WORKSHOP

June 7-9, 2023 | Kailua-Kona, HI

2023 PROGRAM

Photo Credit: Hawaiʻi Tourism Authority (HTA) / Tommy Lundberg

Thank you to our sponsors

This workshop would not have been possible without financial support from our industry and academic partners.

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Program Overview

Day 1 | Clinical Aspects of Breast Density

6:30 AM	Registration & Breakfast
7:30 AM	Oli Blessing & Welcome . . . . page 16
7:40 AM	**Clinical Aspects of Breast Density**
12:00 PM	Lunch
1:00 PM	Adjourn
1:30 PM	Networking Activities . . . . page 22
5:00 PM	Networking Event: Reception @ Papa Kona . . . . page 22
9:00 PM	Networking Activity: Manta Ray Snorkel . . . . page 22

Day 2 | Breast Density Workshop

7:00 AM	Breakfast
8:00 AM	Housekeeping
8:10 AM	**Biology of Breast Density**
10:30AM	**Methods of Density and Risk**
11:40 PM	Lunch
12:40 PM	**Methods of Density and Risk (Continued)**
1:35 PM	**Poster Session 1 (Even Numbers) . . . . page 40**
2:40 PM	**Methods of Density and Risk (Continued)**
4:00 PM	Adjourn
5:30 PM	Networking Event: Island Breeze Luau . . . . page 25

Day 3 | Breast Cancer Risk Assessment

7:00 AM	Breakfast
8:00 AM	Housekeeping
8:10 AM	**Breast Cancer Risk Assessment and Modeling**
11:25 PM	Lunch
12:25 PM	**Breast Cancer Risk Assessment and Modeling (Continued)**
1:20 PM	**Poster Session 2 (Odd Numbers) . . . . page 40**
2:25 PM	**Disparity and Underrepresented Populations**
3:35 PM	Panel Discussion and Questions
3:50 PM	Closing Remarks
4:00 PM	Adjourn

Volpara Scorecard

#1 tool for automated breast density assessment

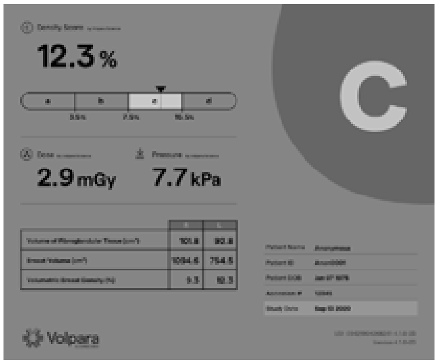
Volpara software is used to assess over 6 million women annually

> 85 million mammography and tomosynthesis images have been deidentified and analyzed by Volpara Health

Volpara has the most scientific papers of all breast radiology AI software companies[1]

The only breast density assessment validated for use with Tyrer-Cuzick 8

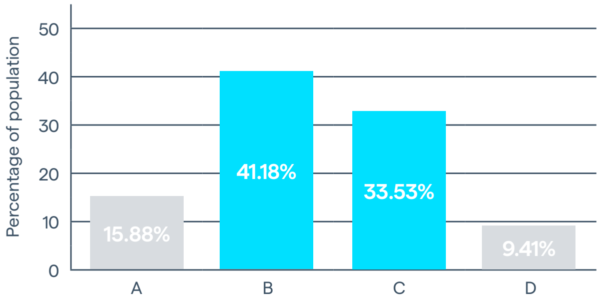
Research has shown that radiologists who assess breast density visually assign density categories inconsistently.[2] The objective TruDensity® algorithm in Volpara® Scorecard™ is proven to reduce reader variability. TruDensity automatically assesses the volumetric breast density percentage (VBD%) of each mammogram on a continuous scale. This differentiates each woman on a continuum of density—whether her density is a "high B" or a "low C." This gives the radiologist important insight to evaluate patients on the dense, non-dense threshold more precisely.



Radiologists typically agree with Volpara's assessment of non-dense (A or B) or dense (C or D) 96% of the time.[3]

Accuracy and consistency are critical to patient density classification

Nearly 75% of patients will be assessed in either the B or C density categories. Accurate classification between a BI-RADS® B and C is essential.



BI-RADS classification of breast density by categories A to D[4]

Two experts agreed about 65% of the time on a BI-RADS density category in a blind study.[5]

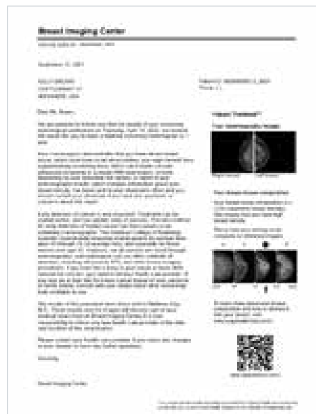
The TruDensity physics-based AI algorithm is cleared by the FDA, Health Canada, and TGA (Australia); is CE marked; and has been validated in more than 400 articles and research abstracts.[1]

Going beyond density inform to understanding + action

The FDA recently announced changes to the Mammography Quality Standards Act (MQSA), making breast density notification a federal requirement, **effective September 10, 2024**.

1. The mammography report summary to patients must identify whether the patient has **dense** or **non-dense** breast tissue and includes a prescribed paragraph on the significance of breast density.
2. Reports for healthcare providers must include an assessment of breast density using the BI-RADS 5th Edition categories.

Volpara® Thumbnail™ empowers patients to understand their breast density with image-enhanced mammography results letters. Patients are shown two non-diagnostic images of their breasts and an explanation of what their density category means in simple-to-understand terms and visuals.



Scan the QR code to learn more.

Volpara Health supports the Find It Early Act

A new federal bill, the **Find It Early Act**, aims to ensure all health insurance plans cover screening and diagnostic breast imaging without out-of-pocket costs for women with dense breasts or higher risk for breast cancer.

Volpara supports improved access to personalized screening and on May 1, 2023, announced that we will donate 5% of the profits from all sales of Volpara Scorecard™ to DenseBreast-Info for the next twelve months for our advocacy efforts. Scan the QR code to learn more.

5% Volpara Scorecard profits donation

1. https://link.springer.com/article/10.1007/s00330-021-07892-z
2. Redondo A, Comas M, Macià F, Ferrer F, Murta-Nascimento C, Maristany MT, Molins E, Sala M, Castells X. Inter- and intraradiologist variability in the BI-RADS assessment and breast density categories for screening mammograms. Br *J Radiol.* 2012 Nov;85(1019):1465–70. doi: 10.1259/bjr/21256379. Epub 2012 Sep 19. PMID: 22993385; PMCID: PMC3500788.
3. Data on company file. Analysis from 36,642 cases across four clinics.
4. Panta, Ritu & Shrestha, Shanta & Jha, Anamika. (2020).
5. Ciatto et al, The Breast 2005. Glandular density distribution in digital mammography. *Grande Medical Journal.* 2. 5-9. 10.3126/gmj.v2i1.45080.

Volpara HEALTH

Workshop Overview

A high amount of dense breast tissue is known to be one of the strongest risk factors for breast cancer. However, the specific reason(s) and mechanisms are not fully understood. Recently the Food and Drug Administration passed a law that will require, starting September 2024, that breast density be reported to healthcare providers and women so they know whether their personal density is low or high and how it might impact breast cancer detection and risk. The US Prevention Task Force recently concluded current evidence is insufficient to assess the balance of benefits and harms of supplemental screening for breast cancer using breast ultrasonography or magnetic resonance imaging (MRI) in women identified to have dense breasts. Breast density is known to differ by race, ethnicity, body mass index, and other clinical risk factors, such that density alone cannot be used to decide on supplemental imaging and requires determining breast cancer risk. Further, the technology and methods to extract quantitative risk and masking information from breast images is rapidly changing with the rapid adaptation of artificial intelligence in medical imaging. For all of these reasons, the study of breast density and risk-based modeling is more relevant than ever.

The International Breast Density & Cancer Risk Assessment Workshop has been held biennially since 2002 and in Hawaiʻi since 2019. We are very happy to resume this important in-person meeting, postponed due to COVID-19. I and my co-chair, Karla Kerlikowske (UC San Francisco), welcome you to the 10th Workshop.

In this workshop, we will explore all aspects of the evolving story of breast cancer risk factors derived from mammography images and how these radiomic biomarkers add to clinical risk factors to determine the overall risk of breast cancer risk and interval and advanced cancer risk. On day one, we will survey what is known and is clinically useful to those on the front line of patient care. On day two, we will go deep into the biology of breast density and novel methods of deriving risk information from imaging. On the last day, we will bring it all together by combining what is known about integrating imaging risk factors with clinical risk factors to predict breast cancer. We have great networking activities planned so you can get to know your colleagues.

Lastly, I hope you take the opportunity to get to know Hawaiʻi Island, also known as the Big Island, on your visit. Explore Kailua-Kona Village, visit Kilauea, one of the world's most active volcanoes, in Volcanoes National Park, meet our advocates, and most importantly discover why Hawaiʻi is an ideal location for this meeting - our need is great, our people are diverse and representative of virtually all continents. Hawaiʻi wants to get to know you and I hope you reach out and get to know us.

Mahalo, John Shepherd - for the Chairs of the Workshop

–
The 1st Breast Densitometry Workshop
San Francisco, CA (2002)

–
The 9th International Breast Density and Cancer Risk Assessment Workshop. Mahalo to Stephanie Rania and Geraldine Ragsac for planning our first IBDW in Hawaiʻi!
Honolulu, HI (2019)

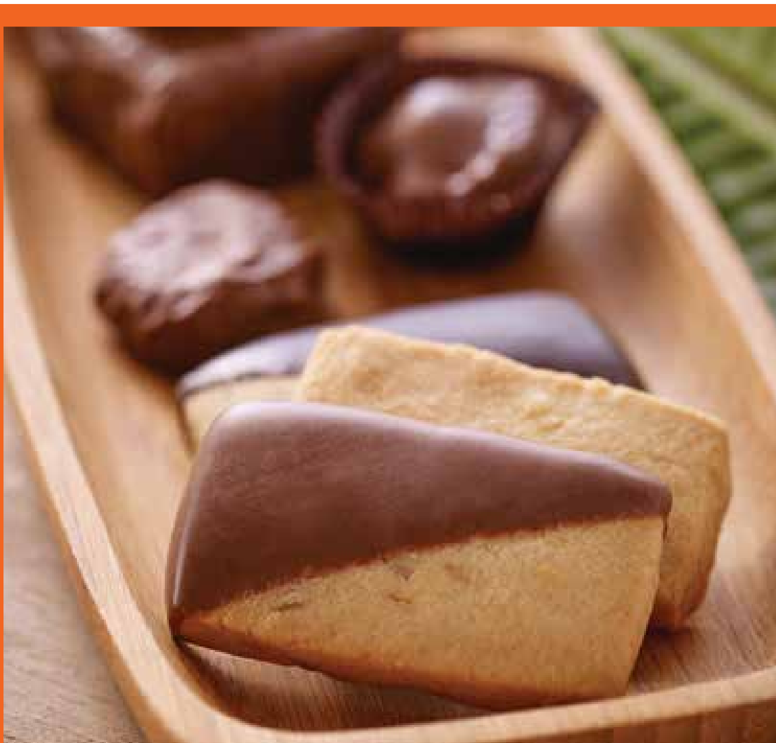
ABOUT OUR HOST - The University of Hawaiʻi Cancer Center

701 Ilalo St, Honolulu HI 96813
uhcancercenter.org

The University of Hawaiʻi Cancer Center (UHCC) is the only National Cancer Institute-designated cancer center in Hawaiʻi and the Pacific. The Center's mission is to reduce the burden of cancer through research, education, patient care and community outreach with an emphasis on the unique ethnic, cultural and environmental characteristics of Hawaiʻi and the Pacific.

It is a state of the art facility that has the ability to attract the best scientists to research cancer, conducting both population-based and laboratory-based research. Their work is unique because they research how cancer affects people with different ethnic, cultural and environmental characteristics. Since Hawaiʻi has one of the most diverse populations in the world, it's an ideal place to study why some ethnic populations are more susceptible to certain cancers and how genetic susceptibility interacts with environmental factors in producing cancer risk.

UNIVERSITY OF HAWAIʻI
CANCER CENTER



General Information

Meeting Room WiFi Access

Network: Marriott Meeting Room
Password: KOACY

Feedback Survey

At the end of the meeting, we welcome your feedback through our feedback survey here:
https://breastdensityworkshop.org/feedback-survey

Security

We urge caution with regard to your personal belongings and syllabus books. We are unable to replace these in the event of loss. Please do not leave any personal belongings unattended anywhere.

Exhibits

Industry exhibits will be available in the Kamakahonu Pre-Function Room during breakfast, breaks, and lunches.

Poster Session and Presenter Information

The poster sessions will take place in the Kamakahonu Pre-Function Room. Session 1 will be held on Thursday, June 8 for the EVEN numbered posters, and Session 2 will be held on Friday, June 9 for the ODD numbered posters. Please look for your poster number on page 40 or at the bottom of the page with your abstract.

Final Presentations

A private link to PDF versions of the final presentations will be sent via email 3-4 weeks after the course.

Conference Committee

Aimee Bowen

Elizabeth Kuioka

and the Shepherd Research Lab staff.

If you have any questions during the conference, feel free to see one of us!

Course Chairs

John Shepherd, PhD
University of Hawai'i Cancer Center

Karla Kerlikowske, MD
UC San Francisco School of Medicine

Scientific Advisory Committee

Kimberly Bertrand, ScD
Boston University School of Medicine

Per Hall, MD, PhD
Karolinska Institutet

Rulla Tamimi, ScD
Weill Cornell Medical College

Celine M. Vachon, PhD
Mayo Clinic Rochester

Leis

Below are the different leis you may see at the workshop. Leis are given in recognition of certain roles at the workshop. If you receive one of these leis, please try to wear it the entire workshop so others know the role you played. It will stay fresh longer if you keep it in your room fridge. Lastly, some lei etiquette — never throw away your lei in the trash — in Hawaiʻi, that is like throwing the gift-giver's affection away. Instead, it is common to discard your lei by throwing it in the ocean, or hanging it in a tree. We will provide a lei "tree" at the end of the meeting to leave your lei if you like. The idea is to return the lei to the area from which it came, which is a sign of respect.

Attendees

Kukui or Mongo Shell

Lei made from kukui nut and mongo sea shells are beautiful and long-lasting. Both materials have been seen as symbols of peace.

Chairs

ʻOkika

(Dendrobium Orchids)

Dendrobium orchids have been among Hawaiʻi's most popular plants since they were introduced from the Philippines in 1896.

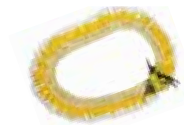
Scientific Advisory Committee

ʻOkika & Ki

(Orchids & Ti plant)

In old Hawaiʻi, Ki was used medicinally. The leaves were wrapped around warm stones to serve as hot packs for injuries.

Invited Speakers



Ilima & ʻawapuhi ʻulaʻula

(White Ginger and Mallow)

Originally from the Himalayas region of Nepal and India, the White Ginger Lily was introduced to Hawaiʻi by early settlers and has since been naturalized.

Poster Speakers

He'e

The red buds grow in clusters that resemble "arms" which is the reason they are called "He'e" the Hawaiian name for octopus.

Staff

ʻOkika

(Dendrobium Orchids)

Orchids have become the single most valuable commercial flower in Hawaiʻi.

Vendor Representatives

ʻOkika

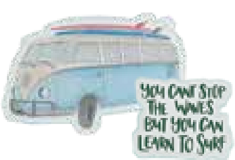
(Dendrobium Orchids)

They are sturdier than most flowers, long lasting, can be dyed and have no scent, making it a flower that is great for lei making.

Name Badge Stickers

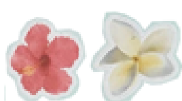
I love SPAM

I've surfed



I've tried poi

Graduate Student

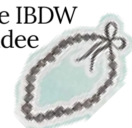


First time presenter

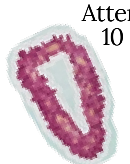
First time in Hawaiʻi

Never had Kona coffee

First time IBDW attendee

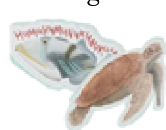


Attended ALL 10 meetings



Looking for a job

Looking to hire



Morning person

Night owl

IBDW 2023 T-Shirts

Orchid Lei

Flower leis are typically given as a welcome to visitors or as a gift of friendship. The orchid lei is one of the most popular leis. Its bright, beautiful flowers are easy to recognize and have a mild scent that everyone can enjoy.

Maile Lei

The maile leaf lei is popularly worn by men, especially for special occasions such as graduation, weddings, or prom. Open leis are also worn by pregnant women, closed leis are considered a symbol of bad luck during pregnancy.

Per Hall, PhD, MD

Professor, Karolinska Institutet, Stockholm, Sweden
Senior Consultant, Department of Oncology, Södersjukhsuet, Stockholm, Sweden

Per Hall is a medical oncologist by training and currently holds positions as Professor of Epidemiology at Karolinska Institutet and as a senior consultant at Södersjukhuset, Stockholm, Sweden.

My focus is prevention and early detection of breast cancer. I established the Karma Cohort, a population based prospective breast cancer screening cohort including 70,000 individuals. I have been the PI of several randomised controlled trials aiming at identifying compounds that lowers the risk of breast cancer (low dose tamoxifen, topical and oral endoxifen) and evaluating supplementary imaging techniques such as contrast enhanced mammography. During my presentation I will describe how we, and others, use mammographic density change as proxy for endocrine therapy response. The next major project will be SMART (Stockholm Mammography Risk stratified Trial). The aim is to test if risk-based screening, including risk assessment and identification of high-risk women, leads to earlier detection of breast cancers compared to the current age-based screening approach.

Noriaki Ohuchi, MD, PhD

Professor, Graduate School of Medicine, Tohoku University

Noriaki Ohuchi, MD, PhD, graduated Tohoku University School of Medicine in 1978, and received PhD degree in 1984. He was assigned as a fellow at Laboratory of Tumor Immunology and Biology, National Cancer Institute, NIH, USA from 1984 to 1986, with promoting cancer genomic research. Then, he was appointed as a professor of Tohoku University in 1999, and deserved as the Director of Cancer Center of University Hospital from 2011 to 2012, and the Dean of Graduate School of Medicine, Tohoku University from 2012 to 2015.

Professor Ohuchi covers many research fields including oncology, surgery, molecular biology and cancer screening with more than 400 original articles published. In summarizing his carrier activities in the field of cancer screening, the following will be selected, e.g., a chief investigator of national breast cancer screening programs supported by Ministry of Health Labour and Welfare (MHLW) of Japan from 1995, and a chairman of national committee on cancer program in Japan from 2012 to present. Also, he has been a member of the International Breast Cancer Screening Network (IBSN, currently ICSN) from 1997.

The Japan Strategic Anti-cancer Randomized Trial (J-START) is one of his representative projects which was supported by MHLW 2007-2014, and by Japan Agency for Medical Research and Development (AMED) 2015-present. He assessed the primary endpoint of the trial that adjunctive ultrasonography to mammography improved sensitivity and detection rates of early breast cancers, as published in the Lancet, 387: 341-348. 2016. As a subanalysis of the primary endpoint, the article describing evaluation of adjunctive ultrasound for breast cancer detection among women aged 40-49 with varying breast density has recently been published in JAMA Network Open. 2021;4(8):e2121505.

At this Workshop, he will talk about J-START, the RCT to assess/evaluate effectiveness of adjunctive ultrasonography in breast cancer screening for women aged 40-49. He will focus on the performance of ultrasonography on the issue with varying breast density.

Ana Pereira Scalabrino, MD, PhD

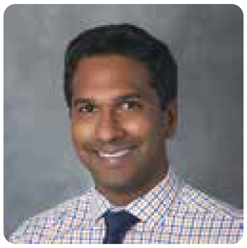
Associate Professor at the Center for Research in Food Environments and Prevention of Nutrition-Related Chronic Diseases, Institute of Nutrition and Food Technology

Ana Pereira is an Associate Professor and epidemiologist at the Center for Research in Food Environments and Prevention of Nutrition-Related Chronic Diseases (CIAPEC) at the Institute of Nutrition, University of Chile. She has conducted epidemiological studies in nutrition and cancer prevention, specifically in breast cancer. Currently, she leads the Growth and Obesity Cohort Study (GOCs), a large longitudinal follow-up of 1190 adolescents born in 2002 in Santiago, Chile. Part of her work has been focused on understanding breast development and its composition during puberty, a critical window of susceptibility for breast cancer risk. She is evaluating how nutrition, body composition, diet, and other environmental factors during infancy determine a higher breast density after the onset of menarche but before the first full-time pregnancy. Furthermore, she has been working on models to optimize breast cancer screening schemes in Chile.

Karla Kerlikowske, MD

Professor of Medicine and Epidemiology and Biostatistics
University of California, San Francisco

Dr. Karla Kerlikowske is Professor of Medicine and Epidemiology and Biostatistics at University of California, San Francisco and primary care physician at the San Francisco Veterans Affairs Health Care System where she co-Directs the Women's Comprehensive Health Care Center and Directs the Women's Health Research fellowship. Her research focuses on breast imaging, breast cancer risk prediction, breast density and epidemiology of invasive breast cancer and DCIS. She is Principal Investigator of the San Francisco Mammography Registry that began collecting breast imaging, risk factor and outcome data in 1994 and participates in the Breast Cancer Surveillance Consortium (BCSC). In addition, she is Co-PI of a BCSC program project grant "Advancing Equitable Risk-based Breast Cancer Screening and Surveillance in Community Practice" that is creating new risk prediction models for screening and surveillance, evaluating AI algorithms for detection and risk prediction, and examining equity of risk models and risk-based screening strategies.



Vignesh A. Arasu, MD, PhD

Kaiser Permanente Division of Research

Vignesh A. Arasu, MD, PhD, is a Research Scientist with the Kaiser Permanente Northern California Division of Research. He is also a practicing radiologist subspecializing in breast imaging at Kaiser Permanente Vallejo Medical Center.

Dr. Arasu conducts research at the intersection of medical imaging, breast cancer, and artificial intelligence (AI). As an embedded clinician researcher, he evaluates priority operational issues in breast cancer medical imaging to accelerate implementation and innovation. As a research principal investigator, he oversees two randomized trials investigating the use of AI for breast cancer screening.

Dr. Arasu earned his medical degree and completed his radiology residency and fellowship at the University of California, San Francisco (UCSF). He also holds a PhD in Epidemiology and Translational Science from UCSF

Adetunji Toriola, MD, PhD

Professor of Surgery,
Division of Public Health Sciences
Department of Surgery
Co-Leader, Cancer Prevention and Control Program
Siteman Cancer Center
William H. Danforth Washington University Physician Scholar
Washington University School of Medicine

Dr. Toriola is a Professor of Surgery in the Division of Public Health Sciences, Washington University School of Medicine, St.Louis, MO, and the William H. Danforth Washington University Physician-Scientist Scholar. He co-leads the Cancer Prevention and Control Program at Siteman Cancer Center. His research focuses on characterizing the molecular basis, and determinants of mammographic breast density and breast cancer to identify those that can be targeted in breast cancer prevention, especially in premenopausal women. He is the Principal Investigator on 2 R01s in this research area, including an NCI MERIT Award. He is leading a phase II clinical trial investigating the impact of RANKL inhibition on mammographic breast density and breast tissue/blood markers in premenopausal women with dense breasts. He is also applying omics platforms to understand the molecular mechanisms underlying mammographic breast density in premenopausal women. Dr. Toriola was awarded the 2022 AACR Outstanding Investigator Award for Breast Cancer Research.

Marike Gabrielson, PhD

Department of Medical Epidemiology and Biostatistics
Karolinska Institutet, Sweden

Marike Gabrielson is a researcher in molecular cancer epidemiology at the Department of Medical Epidemiology and Biostatistics, at Karolinska Institutet, Stockholm, Sweden. Her research focuses on the aetiology of breast cancer and breast cancer risk with an emphasis on the biological mechanisms behind mammographic density as a risk factor for breast cancer. Her current research targets three areas: 1) Understanding the biology of breast cancer risk and identifying biomarkers of risk within the breast and tissue and by hormone and proteomic profiles, 2) Understanding the mechanisms of action of the drug tamoxifen in preventing breast cancer and identifying biomarkers for treatment effects by tamoxifen, and 3) Using biomarkers for tailoring individualised preventive and adjuvant therapy of breast cancer. She is a member of the scientific board in the KARMA breast cancer project (Karolinska Mammography Project for Risk Prediction of Breast Cancer).

Adam Yala, PhD

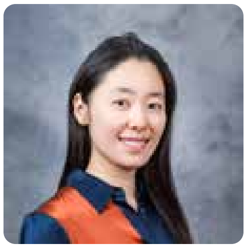
Assistant Professor of Computational Precision Health, EECS UC Berkeley and UCSF

Adam Yala an assistant professor of Computational Precision Health and EECS at UC Berkeley and UCSF. His research focuses on developing machine learning methods for personalized medicine and translating them to clinical care. His previous research has contributed to three areas: 1) predicting future cancer risk, 2) designing personalized screening policies and 3) private data sharing through neural obfuscation. Adam's tools underly multiple prospective trails and his research has been featured in the Washington Post, New York Times, Boston Globe and Wired. Prof Yala obtained his BS, MEng and PhD in Computer Science from MIT and he was a member of MIT Jameel Clinic and MIT CSAIL.

Despina Kontos, PhD (she/her)

Matthew J. Wilson Professor of Research Radiology II
Associate Vice-Chair for Research
University of Pennsylvania, Department of Radiology

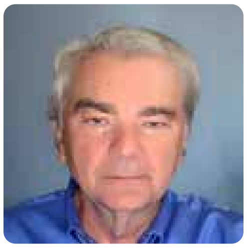
Dr. Despina Kontos, Ph.D., is the Matthew J. Wilson Professor of Research Radiology II and Associate Vice-Chair for Research at the University of Pennsylvania, Department of Radiology. She is a computer scientist by training, with research interests focusing on investigating the role of quantitative imaging as a predictive biomarker for guiding personalized clinical decisions in cancer screening, prognosis, and treatment. Dr. Kontos's lab has pioneered computational approaches for breast cancer risk assessment with digital breast tomosynthesis, including novel volumetric density measures. She is leading several research studies funded by the NIH/NCI and private foundations to incorporate quantitative multi-modality imaging measures of breast tissue composition into cancer risk prediction models.



Shu (Joy) Jiang, PhD

Associate Professor, Division of Public Health Sciences, Department of Surgery,
Washington University School of Medicine in St. Louis

Dr. Jiang is a tenured Associate Professor in the Division of Public Health Sciences at Washington University School of Medicine. She has obtained her PhD in Statistics in 2018 at the University of Waterloo, Canada, and subsequently pursued a postdoctoral fellowship in Biostatistics at Harvard School of Public Health. Her research focuses on the development of novel statistical methods for dynamic risk prediction with censored outcomes, especially on feature extraction in high-dimensional time-varying risk factors and images. She is the principal investigator on the R37 NCI MERIT Award focusing on the statistical methodology for dynamic prediction incorporating time-varying covariates for the onset of breast cancer. This year, Dr. Jiang was recognized as a member of the Forbes 30 under 30 in Healthcare for her development of statistical methods for precision oncology with a particular focus on breast cancer.



Neb Duric, PhD

Professor and Vice Chair of Research
University of Rochester

Neb Duric holds the position of Professor and Vice Chair of Research in the Department of Imaging Sciences at the University of Rochester Medical Center in Rochester, NY, USA. He has championed and used the emerging new imaging modality of ultrasound tomography (UST) to carry out a variety of clinical studies relating to breast cancer detection and risk assessment.

Currently, he is investigating risk factors that can be extracted from UST images, including density and stiffness of breast tissues, as well as features amenable to AI analysis. With recent approval by the FDA for screening of women with dense breasts, UST has the potential to provide the improved risk stratification needed in this population, at time of screening. The long- term goal is to facilitate preventive interventions for high-risk women through integration of UST-based risk factors into clinical risk models for individualized risk assessment.

Celine M. Vachon, PhD

Professor of Epidemiology and Consultant, Mayo Clinic

Dr. Vachon is Consultant and Professor of Epidemiology at the Mayo Clinic, and her research program has focused on genetic and molecular epidemiology of early markers on the carcinogenic pathway to breast cancer and multiple myeloma, including breast density and benign breast disease (BBD) in context of breast cancer. Her work has focused on characterizing breast imaging markers, as risk factors and biomarkers, as well as their genetic epidemiology and contributions to polygenic risk scores and benign breast pathology. More recently, she has collaborated to develop radiomic phenotypes important for breast cancer risk and masking and assess breast AI algorithms for their utility in the clinic setting. She has established and led multiple cohort studies in breast imaging, including the Mayo Mammography Health Study Cohort, the Mayo STRIVE cohort, and a Latina cohort within a federally qualified medical center in Arizona and she serves as the primary epidemiologist on the long-standing Mayo BBD cohort.

Jennifer Stone, PhD

A/Prof, University of Western Australia

A/Prof Jennifer Stone is a cancer epidemiologist/biostatistician and Head of the Genetic Epidemiology Group at the University of Western Australia in Perth, Australia. Her research aims to improve breast cancer screening by accumulating translatable evidence for the clinical use of risk factors, like breast density and body mass index, to tailor screening and improve breast cancer outcomes through early diagnosis and risk-reducing strategies. A/Prof Stone is currently leading a National Health and Medical Research Council (NHMRC) Targeted Call for Research project, BreastScreenPlus, investigating a novel intervention targeting obesity-related barriers to mammographic screening. She is also a Chief Investigator within a NHMRC Centre for Research Excellence investigating Precision Public Health Approaches to Breast Cancer Screening, Early Detection and Mortality Reduction. A/Prof Stone also established (and co-chairs) the Australian Breast Density Consumer Advisory Council in 2019 to provide a community perspective on the research activities across Australian institutions interested in breast density research and breast cancer screening.

Mikael Eriksson, PhD
Department of Medical Epidemiology and Biostatistics
Karolinska Institutet, Sweden

Mikael Eriksson, PhD, is an epidemiologist at Karolinska Institutet in Sweden. Driven by improving mammography screening to reduce breast cancer mortality, Eriksson specializes in developing individualized risk assessment techniques for identifying women who have suboptimal benefit from screening. He studies women in need of additional screening resources and women who may not benefit at all from mammography screening. In addition, Eriksson is working with exciting projects on developing risk models for identifying women who could benefit from risk reducing interventions. In this area, he also develops imaging biomarkers for risk reducing therapy response and studies early indicators for which women may benefit from prophylactic treatment.

Parisa Tehranifar, DrPH
Associate Professor, Epidemiology at Columbia University Irving Medical Center

Parisa Tehranifar is a cancer epidemiologist and health disparities researcher at Columbia University Irving Medical Center, Mailman School of Public Health. Her research broadly aims to address sources of cancer health disparities with a focus on improving breast cancer prevention and screening in racially and ethnically diverse populations. Her research focuses on improving the implementation of breast cancer screening and prevention in racially and ethnically diverse populations. Dr. Tehranifar's current studies focuses on improving the implementation of breast cancer risk assessment, and breast cancer screening and decision making in women with family history of breast cancer and mammographically dense breasts and in older women at average risk for breast cancer.

Kimberly Bertrand, ScD
Associate Professor of Medicine Slone Epidemiology Center at Boston University

Kimberly Bertrand is Associate Professor of Medicine at the Boston University Chobanian & Avedisian School of Medicine and an epidemiologist at the Slone Epidemiology Center at Boston University. Dr. Bertrand's research focuses primarily on the epidemiology of breast cancer, with an emphasis on understanding racial disparities in incidence and outcomes. She is currently Multiple Principal Investigator of the Black Women's Health Study (BWHS), a prospective cohort study of 59,000 self-identified Black women established in 1995. Dr. Bertrand is also Principal Investigator of an R01 grant based in the BWHS to evaluate risk factors for high mammographic density, a strong independent predictor of breast cancer, and the role mammographic density and other risk factors may play in tumor aggressiveness in Black women.

Faculty Disclosures

The following faculty speakers, moderators, and planning committee members have disclosed they have no financial interest/ arrangement or affiliation with any commercial companies who have provided products or services relating to their presentation(s) or commercial support for this education activity:

Noriaki Ohuchi, MD, PhD
Ana Pereira Scalabrino, MD, PhD
Karla Kerlikowske, MD
Vignesh A. Arasu, MD, PhD
Adetunji Toriola, MD, PhD
Marike Gabrielson, PhD
Shu (Joy) Jiang, PhD
Celine M. Vachon, PhD
Jennifer Stone, PhD
Parisa Tehranifar, DrPH
Kimberly Bertrand, ScD

The following faculty speakers have disclosed a financial interest/arrangement or affiliation with a commercial company who has provided products or services relating to their presentation(s) or commercial support for this education activity.

Per Hall, PhD, MD
A license agreement and financial support from iCAD Scientific Advisory Board of Atossa Therapeutics

Adam Yala, PhD
Consulting for Janssen R&D and Merck. Scientific Advisory Board for HuroneAI.

Despina Kontos, PhD
I have institutional research funding from iCAD Inc. and Genmab.

Neb Duric, PhD
Neb Duric is Co-founder of Delphinus Medical Technologies, developer of the imaging modality that will be discussed in this presentation. He has financial interests in the company that are currently being managed by the University of Rochester as part of its Conflict-of-Interest management policy.

Mikael Eriksson, PhD
Grant from Cancer Research KI-Mayo Clinic Cancer Centre Collaborative Grant.
Grant from The Swedish Breast Cancer Association.
Patent on "system and method for assessing breast cancer risk using imagery" with a license to iCAD Medical, Nashua, NH.
Patent on "compositions and methods for monitoring the treatment of breast disorders" with a license to Atossa Therapeutics, Seattle, WA"

Registration
6:30 AM - 7:30 AM ---------- Pre-Function Room

Breakfast
6:30 AM - 7:30 AM ---------- Ballroom 1+2

Sponsored by Volpara Health.

Welcome
7:30 AM - 7:40 AM ---------- Ballroom 3+4

Opening Oli Chant
Kahu Daniel Akaka

Introduction
John Shepherd, PhD, University of Hawaii Cancer Center

Clinical Aspects of Breast Density
Moderator: Karla Kerlikowske
7:40 AM - 9:00 AM ---------- Ballroom 3+4

CLINICAL ASPECTS TALK 1

Mammographic Density *Change*
Per Hall, PhD, MD
Professor, Karolinska Institutet, Stockholm, Sweden
Senior Consultant, Department of Oncology, Södersjukhsuet, Stockholm, Sweden

CLINICAL ASPECTS TALK 2

Adjunctive Ultrasonography for Breast Cancer Screening Among Women Aged 45-49 with Varying Breast Density: A Randomized Controlled Trial, J-START
Noriaki Ohuchi, MD, PhD
Professor, Graduate School of Medicine, Tohoku University

Coffee Break
9:00 AM - 9:30 AM ---------- Pre-Function Room

Clinical Aspects of Breast Density (Continued)
Moderator: Per Hall
9:30 AM - 12:00 PM ---------- Ballroom 3+4

ABSTRACT PROFFERED TALK - POSTER #19

Ultrasound Tomography Measures of Breast Density Decline by Treatment-Associated Endocrine Symptoms After Tamoxifen Therapy: Exploring the Role of CYP2D6 Phenotype and Tamoxifen Metabolites
Cody Ramin, National Cancer Institute and Cedars-Sinai Medical Center

ABSTRACT PROFFERED TALK - POSTER #3

Women's Responses to Breast Density Notifications Vary by Literacy and Sociodemographic Characteristics
Christine Gunn, The Dartmouth Institute for Health Policy and Clinical Practice

CLINICAL ASPECTS TALK 3

Adiposity and Diet During Childhood and Puberty is Associated to Breast Composition During Adolescence: Evidence from the Growth And Obesity Cohort Study (GOCs).
Ana Pereira Scalabrino, MD, PhD
Associate Professor at the Center for Research in Food Environments and Prevention of Nutrition-Related Chronic Diseases, Institute of Nutrition and Food Technology

CLINICAL ASPECTS TALK 4

Breast Density, Obesity, Race and Ethnicity, and Advanced Breast Cancer Risk
Karla Kerlikowske, MD
Professor of Medicine and Epidemiology and Biostatistics
University of California, San Francisco

CLINICAL ASPECTS TALK 5

Comparison of Mammography Artificial Intelligence Algorithms for 5-year Breast Cancer Risk Prediction: An Observational Study
Vignesh A. Arasu, MD, PhD
Kaiser Permanente Division of Research

Lunch
12:00 PM - 1:00 PM - Ballroom 1+2

Afternoon Networking Activities
1:30 PM - 5:00 PM - Various Locations

More information on page 22

Sunset Reception
5:00 PM - 9:00 PM -Papa Kona Restaurant & Bar

More information on page 22

Evening Networking Activity
9:00 PM - 12:00 AM - KONASTYLE

Late Night Manta Ray Snorkel, more information on page 22

Before written language, Hawaiians devised the *oli*, elaborate chants, composed to record important information, e.g. births, deaths, triumphs, losses, good times and bad. Within the overall category of *oli* there are 1) genealogies, 2) tales of powerful chiefs, 3) stories of the beauty of various lands, and 4) expressions of love to woo a potential lover. A chanter oftentimes weaves *kaona* or double-meaning creating three, four, or five different levels of possible translation. So while some may hear the *mele* and think it means one thing, others more familiar with the context would understand a very different interpretation. It is often said that it is nearly impossible to fully understand the meaning of a chant because of this use of *kaona*. Only the intended recipient of the composition would be able to grasp its true meaning.

Hawaiian	English
Onaona i ka hala me ka lehua *He hale lehua nō ia na ka noe*	Fragrant with the breath of hala and lehua This is the sight I long to see
ʻO kaʻu nō ia e ʻanoʻi nei *E li`a nei hoʻi o ka hiki mai*	Of this, my present desire Your coming fills me with eagerness
A hiki mai nō ʻoe *A hiki pū nō me ke aloha*	Now that you have come Loves comes with you
Aloha ē, aloha ē	Greetings, greetings

Daniel "Kaniela" Kahikina Akaka, Jr.

Kahu Hānai, Mauna Lani
Auberge
Resorts Collection

Daniel "Kaniela" Kahikina Akaka, Jr. was born & raised in Nuʻuanu and Pauoa Valleys. He attended the Kamehameha Schools for 13 years. His educational career continued at the University of Hawaiʻi where he received a Bachelors degree in the Hawaiian Studies Program.

Mr. Akaka is presently employed at the Mauna Lani Auberge Resorts Collection on the Island of Hawaiʻi, as the Kahu Hānai of the Living Culture Department. His position at the resort allows him to share the history and culture of Hawaiʻi with the hotel guests as well as the many school groups that come to Mauna Lani to learn about Hawaiian aquaculture as well as the history and stories of this ancient land known as Kalāhuipua'a.

Although he has been employed at Mauna Lani for over 40 years, his business career has also included Aloha Airlines, Hawaiian Holidays, Hawaiian Foliage & Landscaping, the Hawaiʻi Maritime Center, as well as, held the position of Director of Corporate Affairs for American Hawaiʻi Cruises.

Mr. Akaka comes from a family of seven, which include his parents, Daniel (deceased) and Millie Akaka. He and his wife, formerly Anna Lui-Kwan (KS Class '72), have chosen Kona to be their home. They have 5 children, one daughter, four sons and 2 grandchildren with one more on the way.

In keeping with the Hawaiian culture, he has had the opportunity to be a crewmember of the Hokuleʻa for three of its voyages. His first voyage with the canoe was in 1995 along the Pacific Northwest with his wife, Anna, in attendance. His second voyage was in 1999 in which he participated on the second leg of the voyage to Rapa Nui. His 3rd voyage was the completion of the voyage, Kū Holo Lā Komohana, which ended its journey in Yokohama, Japan. His position on the canoe was as the Protocol Officer. Mr. Akaka was also honored to be a participant on other canoe projects which included the making of the "Mauloa" canoe as well as working on the construction and sailing on the double-hulled canoe "Makaliʻi". The last canoe project was the making of the canoe, "Laulima", which was a 2 year cultural project for Mauna Lani and which was made in its entirety at the Hālau Wa'a o Keawanui.

In his work today, Mr. Akaka is involved in perpetuating the culture, the essence, and the Spirit of Hawaiʻi.

Mammographic Density *Change*

Hall, Per[1]; Eriksson Mikael[2]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, and Department of Oncology, Södersjukhuset, Stockholm, Sweden [per.hall@ki.se], [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet.

INTRODUCTION

I have been asked to talk about mammographic density *change*. The most studied mammographic feature is density. The initial qualitative classification of mammographic features was published nearly 50 years ago by Wolfe [1], later modified by Tabar [2]. Norman Boyd took the next steps when developing a computer-assisted technique of measuring mammographic densities [3]. More recently artificial intelligence based methods for identifying features beyond density have been published, both for ordinary 2D mammograms [4] and digital breast tomosynthesis [5].

Mammographic density *change* has attracted increasing interest. Changes in mammography density can occur over time due to various factors, including age, hormonal fluctuations, and certain medical interventions. Hormonal changes during different stages of a woman's life, such as pregnancy, and menopause, affects mammography density. Mammographic features, or patterns, have been used as proxy endpoints for breast cancer in etiologic research as well as in adjuvant treatment and prevention trials.

OBJECTIVES

I will talk about challenges of measuring density change. Density measured from the same woman could vary between different images due to non-physiological technical factors. One way of reducing the technical influences is aligning images before density is measured and compared. I will also talk about how density changes over life, what influences density change over life and how density change over life influences breast cancer risk.

Mammographic density decreases over life, a physiological process called involution. We know fairly well the factors that influences mammographic density but what are the determinants of density change over life [6]? Intuitively women who decrease in density should have a lower risk of breast cancer, but data are conflicting.

Tamoxifen and its metabolites decrease mammographic density and could be used as a proxy for breast cancer therapy response. We have used the density change as an outcome in several trials [7]. Finally, what influence would a mammographic density decrease possibly have on the performance of a mammogram? Is it possible to increase the sensitivity of the diagnostic procedure [8]?

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ADJUNCTIVE ULTRASONOGRAPHY FOR BREAST CANCER SCREENING AMONG WOMEN AGED 40-49 WITH VARYING BREAST DENSITY: A RANDOMIZED CONTROLLED TRIAL, J-START

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[1]Department of Breast and Endocrine Surgical Oncology, Tohoku University Graduate School of Medicine
[2]Department of Breast and Endocrine Surgery, Tohoku Medical and Pharmaceutical University

INTRODUCTION:

Mammography has limited accuracy in breast cancer screening especially for young women. Ultrasonography, when used in conjunction with mammography, is helpful to detect early stage and invasive malignancy for asymptomatic women. To investigate efficacy of supplemental ultrasonography, a large scale randomized controlled trial (RCT) on effectiveness of ultrasound screening for women aged 40-49 was conducted by the Japan Strategic Anticancer Randomized Trial (J-START). Participants were randomly assigned in a 1:1 ratio to undergo either by mammography with ultrasound (intervention arm) or by mammography alone (control arm). Between July 2007 and March 2011, 76,119 asymptomatic women were enrolled. As a result of primary endpoint, supplemental ultrasonography increased sensitivity and detection rate, with more screen-detected cancers of early stage.

OBJECTIVES

To evaluate the performance of adjunctive ultrasonography to mammography, the data on each screening modality according to difference in breast density were analyzed.

METHODS:

This is a sub-study of the J-START, with analyzing 19,213 cases enrolled in Miyagi prefectures during 2007-2020. Sensitivity, specificity, recall rates, biopsy rates, characteristics of screen-detected cancers and interval breast cancers were evaluated between study groups, and each modality according to breast density.

RESULTS:

Out of 19,213 women, 11,390 (59.3%) had heterogeneously or extremely dense breasts. Among the overall group, 130 cancers were found. Sensitivity was significantly higher in the intervention group than the control group (93.2% vs 66.7%; p<.001); a similar trend was observed in dense breasts (93.2% vs 70.6%; P<.001) and non-dense breast (93.1% [vs 60.9%; P<.001). The interval cancers were lower in the intervention group compared with the control group (0.5‰ vs 2.0‰; P=.004). Within the intervention group, the number of invasive cancers detected by ultrasonography alone was statistically higher than mammography alone in both dense and non-dense breasts. However, sensitivity of mammography or ultrasonography alone did not exceed 80% across all breast density in two groups. Comparing with control group, specificity was significantly lower (86.8% [95% CI 86.2–87.5] vs 91.8% [95% CI 91.2–92.3]; P<.001); and recall rates (13.8% vs 8.6%; p<.001) and biopsy rates (5.5% vs 2.1%; P <.001) were significantly higher in intervention group.

CONCLUSION:

Screening mammography demonstrated lower sensitivity, whereas adjunctive ultrasonography to mammography increased sensitivity, with improving detection of early stage and invasive cancers across dense and non-dense breasts.

What is the key finding new since 2019?

Performance of ultrasonography according to breast density category was analyzed in asymptomatic women aged 40-49.

How does this finding impact screening strategies for women?

Adjunctive ultrasonography may be considered as an appropriate imaging modality for breast cancer screening in asymptomatic women aged 40-49 regardless of breast density.

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ADIPOSITY AND DIET DURING CHILDHOOD AND PUBERTY IS ASSOCIATED TO BREAST COMPOSITION DURING ADOLESCENCE: EVIDENCE FROM THE GROWTH AND OBESITY COHORT STUDY (GOCS).

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INTRODUCTION:

Breast density (BD) is largely determined during puberty and tracks thereafter[1]; however, a particularly relevant period for carcinogenesis is the time between menarche and first birth because undifferentiated breast tissue is more vulnerable to environmental exposures. In adults, adiposity and other dietary factors have been linked with BD. However, data on these exposures during the critical window of puberty-first birth is still lacking.

OBJECTIVES:

We have performed repeated BD measurements in 400 Chilean girls from early puberty until 19 years using DXA. Our aims are 1) to describe breast composition during puberty, 2) to assess the association between childhood adiposity trajectories and BD and 3) To assess the role of dietary factors in BD at 2 and 4 years after menarche onset.

METHODS:

GOCS is an ongoing cohort of low-middle income girls born in 2002-2003 in Santiago, Chile who were evaluated from age 4 until age 19. We have routinely collected data on: anthropometry (weight, height, waist circumference (WC)), 24-hour dietary recall data (24HR), sexual maturation, blood biomarkers, and breast composition by DXA (at Tanner 4, and 1, 2 and 4 years after menarche onset).

RESULTS:

The mean age of thelarche onset was 9.2y and of menarche 11.9y (sd=1.1)[2]. The % of fibroglandular volume (%FGV) increased across breast Tanner stages and peaked 250 days after menarche. The absolute fibroglandular volume (AFGV) peaked at 2 years after menarche onset. Girls in the highest quartiles of %FGV and AFGV at Tanner B4 had the highest values thereafter. Lower age of thelarche and menarche onset and longer time between these 2 periods are associated with higher %FGV and AFGV at 1 year after menarche onset.
In linear regression models, we observed that girls who had trajectories of higher body mass index (BMI) and WC during childhood and puberty had higher AFGV at 2 years after menarche onset (b=61.9 (95%CI: 12.9; 110.9) and b= 55.1 (95%CI: 17.4; 92.8), respectively) * compared to girls with the lowest trajectories.
We observed that higher consumption of yogurt (T3vs T1, b= -10.2 (95%CI: -20.2; -0.3)[3] and phytoestrogen intake (Q4vsQ1: -36.19 (95%CI:-66.24, -6.14)[4] during puberty were associated inversely with AFGV at Tanner4*. While girls with higher consumption of high energy foods had higher %FGV (b=0.08 (95%CI:0.01;0.15)) and AFGV (b= 0,17 (95%CI: 0.06;0.29))* 2 years after menarche.
**(models adjusted by: BMI, puberty and socioeconomic level).*

CONCLUSION:

Puberty is a key period for breast development. Adiposity and dietary intake during this period of susceptibility are important factors associated to higher BD at young ages.

What is the key finding new since 2019?

Trajectories of higher BMI and WC and intake of phytoestrogens intake and foods high in energy determines BD at adolescence.

How does this finding impact screening strategies for women?

Maintaining a healthy weight and diet during childhood and puberty could be early strategies for breast cancer prevention.

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Breast Density, Obesity, Race and Ethnicity, and Advanced Breast Cancer Risk

[1]Kerlikowske, K; [2]Chen, S; [2]Bissell, MCS; [3]Lee, CI; [4]Tice, JA; [5]Sprague, BL; [2]Miglioretti, DL.
[1]General Internal Medicine Section, Department of Veteran Affairs and Departments of Medicine and Epidemiology and Biostatistics, [2]Department of Public Health Sciences, University of California, Davis, [3]Department of Radiology, University of Washington, Fred Hutchinson Cancer Center, Seattle, [4]Division of General Internal Medicine, University of California San Francisco, [5]Departments of Surgery and Radiology, University of Vermont Cancer Center

INTRODUCTION:

Advanced breast cancer is a surrogate for breast cancer mortality. Knowledge of personal and clinical risk factors associated with an advanced cancer (prognostic pathologic stage IIA or higher) diagnosis among routine screeners would inform risk prediction models and primary prevention.

OBJECTIVES:

To describe a cumulative 6-year advanced breast cancer risk prediction model and the population-attributable risk proportions (PARP) for advanced stage breast cancer by race and ethnicity and personal and clinical risk factors.

METHODS:

The Breast Cancer Surveillance Consortium (BCSC) cohort was used to develop the 6-year cumulative advanced cancer risk model[1] and to calculate advanced cancer PARPs by race and ethnicity among individuals undergoing annual or biennial screening. Advanced cancer is defined as American Joint Commission on Cancer prognostic pathologic stage IIA or higher.[2]

RESULTS:

Will present:

- Rationale for evaluating advanced breast cancer as primary outcome for risk prediction among routine screeners.
- Definition of advanced cancer
- Advanced cancer risk model
- Population attributable risk proportions for advanced cancer by race/ethnicity and clinical risk factors

CONCLUSION:

Calculating advanced cancer risk can guide patient/provider discussions on screening interval and supplemental imaging among women undergoing routine screening. Primary prevention should focus on shifting overweight and obese women to normal weight to reduce advanced cancer risk.

What is the key finding new since 2019?

Dense breasts and overweight/obesity are the strongest risk factors for advance cancer among routine screeners and prevalence varies by race and ethnicity.

How does this finding impact screening strategies for women?

Women at low/average risk of advanced cancer may undergo biennial screening mammography while those at intermediate or high advanced cancer risk may consider annual screening with or without supplemental imaging.

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Comparison of Mammography Artificial Intelligence Algorithms for 5-year Breast Cancer Risk Prediction: An Observational Study

Arasu VA, Habel LA, Achacoso NS, Buist DS, Cord JB, Esserman LJ, Hylton NM, Glymour MM, Kornak J, Kushi LH, Lewis DA, Liu VX, Lydon CM, Miglioretti DL, Navarro DA, Pu A, Shen L, Sieh W, Yoon HC, Lee C

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INTRODUCTION:

Although several clinical breast cancer risk models are used to guide screening and prevention, they have only moderate discrimination.We compared selected existing mammography artificial intelligence (AI) algorithms to each other and the Breast Cancer Surveillance Consortium (BCSC) risk model for prediction of 5-year risk.

METHODS:

This retrospective case-cohort study included data about women with a negative screening mammogram (no visible evidence of cancer) in 2016, who were followed until 2021, from Kaiser Permanente, Northern California. Women with prior breast cancer or a highly penetrant gene mutation were excluded. Of the 324 009 eligible women, a random subcohort was selected without regard to cancer status, to which all additional cancer cases were added. The index screening mammogram was used as input for five different AI algorithms to generate continuous scores that were then compared with the BCSC clinical risk score. Risk estimates for incident breast cancer 0 to 5 years after the initial mammogram were calculated using time-dependent area under the receiver operating characteristic curve [AUC(t)].

RESULTS:

The subcohort included 13 628 women, of whom 193 had incident cancer. Incident cancers among all eligible women (additional 4391/324 009) were also included. For incident cancers at 0 to 5 years, the AUC(t) for BCSC was 0.61 (95% CI: 0.60, 0.62). All AI algorithms had higher AUC(t)s than BCSC, ranging from 0.63-0.67 (Bonferroni-adjusted P < 0.0016). AUC(t)s for combined BCSC and AI models were slightly higher than AI alone [AI + BCSC AUC(t) range, 0.66 – 0.68, Bonferroni-adjusted P < 0.0016].

CONCLUSION:

When using a negative screening exam, AI algorithms performed better than the BCSC risk model for predicting breast cancer risk at 0 to 5 years. Combined AI and BCSC models further improved prediction.

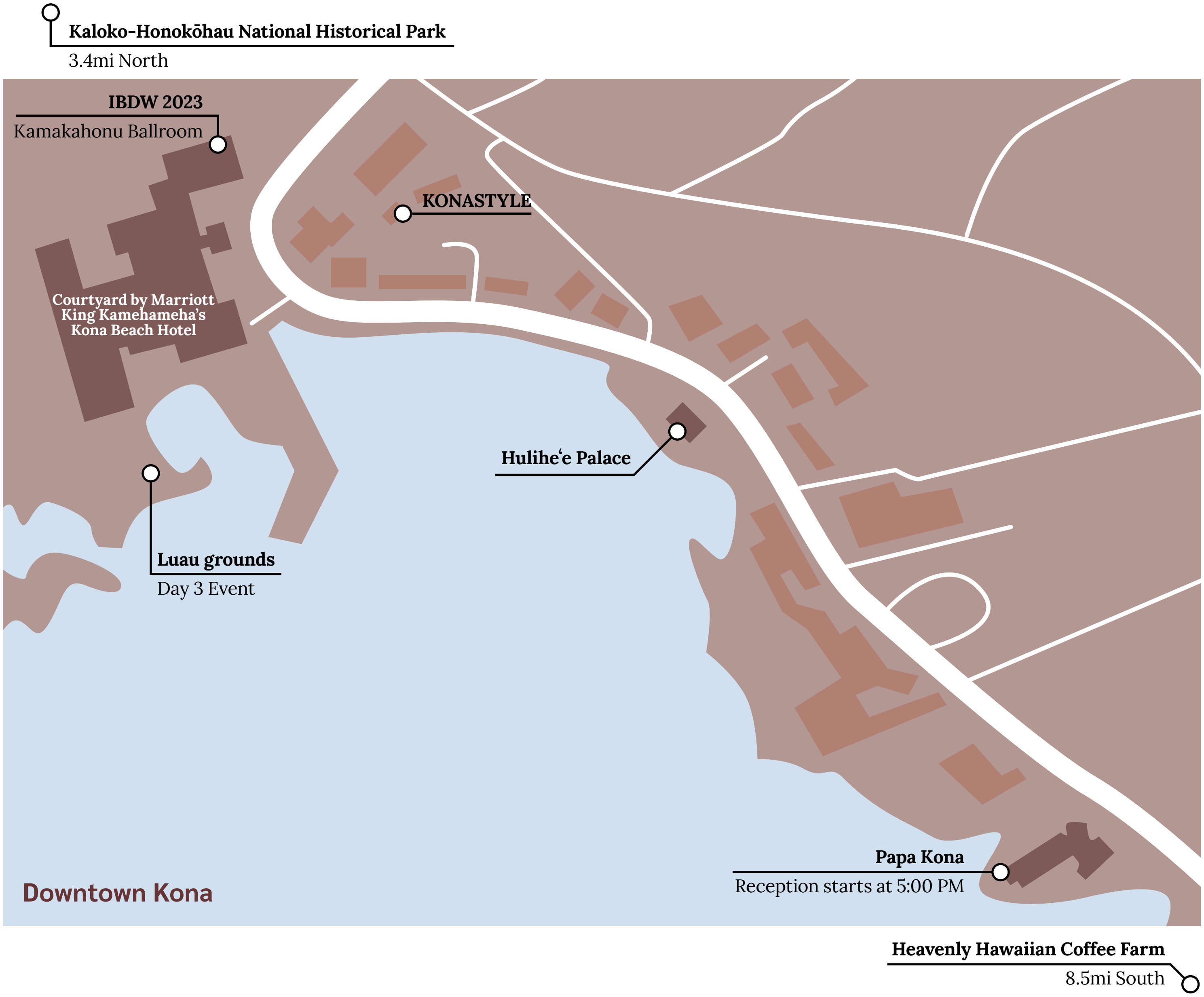
What is the key finding new since 2019?

Negative screening mammograms were analyzed with five artificial intelligence (AI) algorithms; all predicted breast cancer risk to five years better than the BCSC clinical risk model.

Table 1. AUC(t) performance risk models using negative index screening mammograms

Model	Model training time horizon	Interval cancer risk 0 - 1 year (*n* = 259)	Future cancer risk >1 - 5 years (*n* = 4089)
BCSC (Clinical)	0.5 - 5 years	0.62 (0.59, 0.66)	0.61 (0.60, 0.62)
Mirai (MIT, AI)	0 - 5 years	0.68 (0.65, 0.72) 0.002	0.67 (0.66, 0.68) <0.001*
MammoScreen (Therapixel, AI)	0 - 2 years	0.71 (0.68, 0.75) <0.001*	0.65 (0.64, 0.66) <0.001*
ProFound AI (iCAD, AI)	0 - 2 years	0.67 (0.63, 0.70) 0.023	0.65 (0.64, 0.66) <0.001*
Mia (Kheiron, AI)	0 - 1 years	0.71 (0.67, 0.74) <0.001*	0.63 (0.62, 0.64) 0.002
GMIC (NYU, AI)	0 - 0.25 years	0.68 (0.64, 0.71) 0.01	0.64 (0.63, 0.65) <0.001*

* Bonferroni-corrected $P < 0.0016$, as compared with the BCSC clinical risk model



Visiting the Dutch Windmill at the 8th IBDW
San Francisco (2017)
—

Welcome reception for the 6th IBDW
San Francisco (2013)
—

Activities

We have a number of activity suggestions for you to experience Kona alongside your colleagues. Remember to take commemorative photos and post them online with the tag #IBDW2023

Optional Activities

Kona Boys Beach Shack

Located on the beach by the hotel, Kona Boys offers rentals for everything you'll need to enjoy the water. Visit the booth to rent snorkel gear, stand-up paddle boards, kayaks, and more.

Hulihe'e Palace

About a 5 minute walk from the hotel is a beautiful historical site, open until 3:00 PM for self-guided tours.

Kaloko-Honokōhau National Historical Park

A hike through volcanic rock towards historical sites built by native Hawaiians. For anyone looking for a physical activity through Hawaiʻi's unique landscape. (Transportation available, first come first serve.)

Heavenly Hawaiian Coffee Farm (78-1136 Bishop Rd, Holualoa, HI 96725)

Tours and classes at a real Kona coffee farm. Try coffee samples and learn about the history and process of creating Kona Coffee. Purchase tickets on the farm's website. (Transportation available, first come first serve.)

KONASTYLE Late Night Manta Ray Snorkel (9:30 PM)

Book your spot by calling (808)936-1323. Meet at the KONASTYLE shop by 9:00 PM. The group will depart for the snorkeling spot at 9:30 PM and return around midnight.

Reception @ Papa Kona 5:00 PM - 9:00 PM

The Waterfront Row
75-5770 Aliʻi Dr 1st Floor
Kailua-Kona, HI 96740

We will be hosting a sunset reception at Papa Kona Restaurant & Bar, which has beautiful views of the ocean and the sunset. The reception will be located on the second floor of the restaurant.

Accessibility — Please let a staff member know if you need assistance going up to the second floor. There is ramp access to the parking lot, where you may use an elevator to the reception.

Parking — There is parking available underneath the Waterfront Row Shopping Center. Use the machine near the elevators to pay for parking.

Transportation — We recommend walking through Downtown Kona to the reception but staff is available to give rides to and from the reception.

Breakfast

7:00 AM - 8:00 AM - Ballroom 1+2

Sponsored by Volpara Health.

Housekeeping

8:00 AM - 8:10 AM - Ballroom 3+4

Biology of Breast Density

Moderator: Celine Vachon

8:10 AM - 10:00 AM - Ballroom 3+4

PLENARY TALK 1

RANKL Signaling and Mammographic Breast Density in Premenopausal Women

Adetunji Toriola, MD, PhD
Professor of Surgery,
Division of Public Health Sciences
Department of Surgery
Co-Leader, Cancer Prevention and Control Program
Siteman Cancer Center
William H. Danforth Washington University Physician Scholar
Washington University School of Medicine

ABSTRACT PROFFERED TALK - POSTER #12

Associations of Stem Cell Markers CD44, CD24, and ALADH1A1 in Benign Breast Biopsies with Mammographic Breast Density

Rulla Tamimi, Weill Cornell Medicine

ABSTRACT PROFFERED TALK - POSTER #32

Stromal Disruption on Histologic Sections Impairs Tamoxifen-Associated Mammographic Density Reduction and Portends Poor Prognosis in Estrogen Receptor-Positive Breast Cancer

Mustapha Abubakar, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health

PLENARY TALK 2

Molecular Mechanisms of Tamoxifen-Induced Mammographic Density Change – Results from the KARISMA Randomized Clinical Trial

Marike Gabrielson, PhD
Department of Medical Epidemiology and Biostatistics
Karolinska Institutet
Sweden

Coffee Break

10:00 AM - 10:30 AM - Pre-Function Room

Sponsored by Delphinus Medical Technologies.

Methods of Density and Risk

10:30 AM - 11:40 AM - Ballroom 3+4

ABSTRACT PROFFERED TALK - POSTER #8

Interim Results from ScreenTrustMRI - A Randomized Clinical Trial Using a Combination of AI Models as a Selection Tool for Supplemental MRI

Fredrik Strand, Karolinska Institutet

ABSTRACT PROFFERED TALK - POSTER #9

Association of Breast Cancer with a Fully-Automated Measure of Background Parenchymal Enhancement

Gordon Watt, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center

PLENARY TALK 3

Machine Learning Methods for Image-Based Personalized Cancer Screening

Adam Yala, PhD
Assistant Professor of Computational Precision Health, EECS UC Berkeley and UCSF

Lunch
11:40 AM - 12:40 PM -- Ballroom 1+2

Methods of Density and Risk (Continued)
Moderator: Kimberly Bertrand

12:40 PM - 1:35 PM -- Ballroom 3+4

PLENARY TALK 4

Beyond Mammographic Density: Novel Radiomic Phenotypes and 3D Breast Density Measures

Despina Kontos, PhD (she/her)
Matthew J. Wilson Professor of Research Radiology II
Associate Vice-Chair for Research
University of Pennsylvania, Department of Radiology

ABSTRACT PROFFERED TALK - POSTER #47

Artificial Intelligence Predicts Mammographic Breast Density from Clinical Breast Ultrasound Images

Arianna Bunnell, University of Hawaii Cancer Center

Poster Session 1 + Coffee Break
1:35 PM - 2:35 PM -- Pre-Function Room

EVEN NUMBERS - View Poster Numbers and Abstracts on page 40

Methods of Density and Risk (Continued)
2:40 PM - 4:00 PM -- Ballroom 3+4

PLENARY TALK 5

Longitudinal Analysis of Breast-Specific Density Change Assessed by Digital Mammogram is Associated with Breast Cancer

Shu (Joy) Jiang, PhD
Associate Professor, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine in St. Louis

PLENARY TALK 6

Ultrasound Imaging Markers of Breast Cancer Risk

Neb Duric, PhD
Professor and Vice Chair of Research
University of Rochester

Public Session
4:00 PM - 5:00 PM -- Pre-Function Room

Doors will be open for members of the community to view posters.

Evening Networking Activity
5:30 PM - 8:00 PM -- Island Breeze Luau

The Island Breeze Lūʻau at the Courtyard Marriott King Kamehameha's Kona Beach Hotel begins with check-in at 5:30 pm at the luau grounds. Follow the sidewalk near the hotel beach to the gated entrance of the luau grounds.

Lū'au Schedule:

5:30 pm - Check-in (at the luau grounds)
Open bar begins when luau grounds open
Royal Court arrival
Luau dinner buffet
Polynesian Revue - He ʻOhana Kakou

Festivities end at approximately 8:00 pm.

RANKL SIGNALLING AND MAMMOGRAPHIC BREAST DENSITY IN PREMENOPAUSAL WOMEN

Adetunji T. Toriola
Department of Surgery, Division of Public Health Sciences, and Siteman Cancer Center, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8100 St. Louis, MO, 63110, USA

INTRODUCTION:

High mammographic breast density is a strong risk factor for breast cancer, especially in premenopausal women where up to 29% of breast cancer cases are attributable to having dense breasts. A high mammographic density also reduces mammogram sensitivity. Hence, understanding the biological mechanisms underlying high mammographic density could translate to targeted breast cancer prevention. However, adult lifestyle modifications have not been shown to reduce mammographic breast density. Therefore, identifying pathways that can be targeted to reduce breast density and breast cancer incidence with minimal side effects is crucial. The receptor activator of nuclear factor-κB (RANK) pathway plays essential roles in breast development, regulates the development of the lobulo-alveolar mammary structures during pregnancy, and activates downstream signaling cascades involved in breast cancer development and could be a biologically feasible target.

OBJECTIVES:

Our objectives are to investigate the associations of the RANK pathway with mammographic breast density in premenopausal women.

METHODS:

We performed a series of observational studies showing the associations of breast tissue receptor activator of nuclear factor-κB (RANK) gene expression (N=48), as well as circulating RANK and RANK ligand (RANKL) levels (N=365) with mammographic density in premenopausal women. Building on findings from the observational studies, we initiated a pilot phase 1, non-randomized clinical trial (NCT03629717) to investigate the effect of RANKL inhibition on breast tissue markers in high-risk women with dense breasts.

RESULTS:

Both breast tissue RANKL gene expression and circulating RANKL levels are positively associated with mammographic breast density in premenopausal women in observational studies.

Findings from our phase I clinical trial also showed that RANKL inhibition resulted in regulation of signaling pathways essential for hormone, fatty acid metabolism, proliferation, immune regulation and osteoclast differentiation. For instance, gene expression of UDP Glucuronosyltransferase Family 2 Member B15, which plays a role in the regulation of estrogens and androgens as well as aldo-Keto Reductase Family 1 Member B15, which enables estradiol 17-beta-dehydrogenase activity were strongly downregulated.

CONCLUSION:

Our findings support a role of RANKL signaling in dense breasts. RANKL inhibition is a potentially novel path to reducing mammographic breast density, and possibly breast cancer incidence in select high-risk women with dense breasts.

What is the key finding new since 2019?

We have demonstrated associations of the RANKL signaling with mammographic breast density in premenopausal women. A phase II randomized clinical trial (NCT04067726) to quantify the effect of RANKL inhibition on mammographic breast density and breast tissue markers in premenopausal women with dense breasts is currently underway.

How does this finding impact screening strategies for women?

A reduction in mammographic breast density will improve mammogram sensitivity and could result in cancer detection at early stages.

MOLECULAR MECHANISMS OF TAMOXIFEN-INDUCED MAMMOGRAPHIC DENISTY CHANGE – RESULTS FROM THE KARISMA RANDOMISED CLINICAL TRIAL

[1]Gabrielson, Marike; [2]Göransson, S; [3]Dahl, L; [1]Hammarström, M; [1]Czene, K; [1,4]Hall, P.

[1]Department of Medical Epidemiology and Biostatics, Karolinska Institutet, Stockholm, Sweden, [2]Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden, [3]Science for Life Laboratory, Department of Protein Science School of Engineering Sciences in Chemistry, Biotechnology and Health, KTH Royal Institute of Technology, Stockholm, Sweden, [4]Department of Oncology, Södersjukhuset, Stockholm, Sweden

INTRODUCTION:

Tamoxifen prevents recurrence of breast cancer and is suggested for preventive risk-reducing therapy. Tamoxifen reduces mammographic density, a proxy for therapy response, but little is known about its effects in remodelling normal breast tissue. We have previously shown that tamoxifen at doses as low as 2.5 mg/day decreases the mammographic density equally as effective as the conventional dose of 20 mg/day in healthy premenopausal women[1].

OBJECTIVES:

Investigate how tamoxifen at different doses influences the breast tissue composition and expression of tissue and plasma proteomic markers in healthy women. To identify factors that influences the effect of tamoxifen on density change.

METHODS:

This is a substudy within the double-blinded dose-determination trial KARISMA. We investigated tamoxifen-specific changes in breast tissue composition and histological markers in 83 healthy women randomised to 6 months daily intake of 20, 10, 5, 2.5, 1 mg of tamoxifen or placebo. Ultrasound-guided biopsies were collected before and after tamoxifen exposure. Mammographic density, histological breast tissue composition and proteomic markers were measured at baseline and end-of-tamoxifen-exposure. The plasma proteome was also investigated in 44 study participants treated with 20 mg/day tamoxifen and 44 participants on placebo.

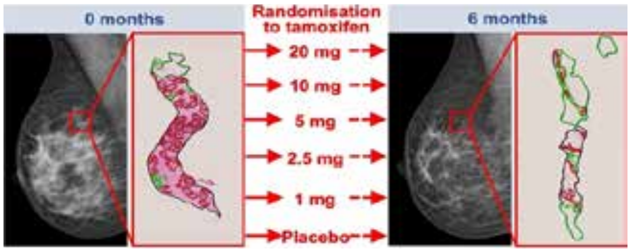


Figure 1. KARISMA biopsy study design.

RESULTS:

High-dose (10-20 mg) and low-dose (2.5-5 mg) tamoxifen reduced mammographic density and glandular-epithelial area in premenopausal women and associated with reduced epithelium and increased adipose tissue. High-dose tamoxifen also decreased epithelial estrogen receptor (ER) and progesterone receptor (PR) expressions in premenopausal women. Premenopausal women with the greatest reduction in proliferation had the greatest epithelial reduction. In postmenopausal women, high-dose tamoxifen decreased the epithelial area with no measurable density decrease. Tamoxifen 20 mg also comprehensively altered the plasma proteome.

Women with the greatest epithelial proliferation and expression of stromal PR at baseline also had the largest density decrease after tamoxifen. Both markers were highly associated with younger age and premenopausal status.

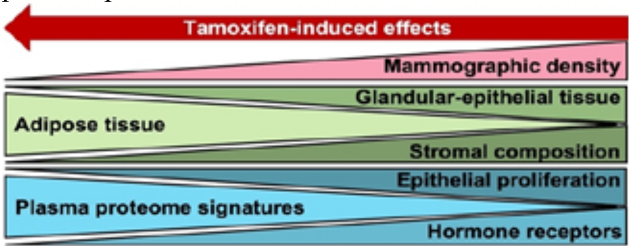


Figure 2. Tamoxifen remodels the breast tissue composition and expression of proliferation and protein markers.

CONCLUSION:

Tamoxifen at both low and high doses influences breast tissue composition and expression of histological markers in the normal breast[2]. Our findings connect epithelial proliferation with tissue remodelling in premenopausal women and provide novel insights to understanding biological mechanisms of primary prevention with tamoxifen.

What is the key finding new since 2019?

Tamoxifen induces comprehensive effects on breast tissue composition and circulating markers associated with mammographic density change.

REFERENCES:

1. Eriksson M, Eklund M, Borgquist S, et al. Low-Dose Tamoxifen for Mammographic Density Reduction: A Randomized Controlled Trial. *J Clin Oncol* 2021: JCO2002598.

2. Gabrielson M, Hammarström M, Bäcklund M, et al. Effects of tamoxifen on normal breast tissue histological composition: Results from a randomised six-arm placebo-controlled trial in healthy women. *Int J Cancer* 2023.

MACHINE LEARNING METHODS FOR IMAGE-BASED PERSONALIZED CANCER SCREENING

[1]Yala, Adam
[1]Computational Precision Health, UC Berkeley and UCSF.

INTRODUCTION:

Screening programs must balance the benefit of early detection with the cost of over-screening. This capacity builds on two complementary technologies: (1) the ability to accurately assess patient risk at a given time point and (2) the ability to design screening regimens based on this risk.

OBJECTIVES:

Our first objective is to develop robust image-based tools for breast cancer risk, and to validate their performance across diverse populations. On second objective is to develop a computational framework for optimizing risk-based screening policies and then to validate the performance of AI-derived guidelines in simulation studies.

Table 1: Performance of Mirai across test sets

Test Set	Uno C-Index	95% confidence
MGH, USA	0.75	(0.72, 0.78)
Novant, USA	0.75	(0.70, 0.80)
Emory, USA	0.77	(0.75, 0.79)
Macabi-Assuta, Israel	0.77	(0.73, 0.81)
Karolinska, Sweden	0.81	(0.79, 0.82)
CGMH, Taiwan	0.79	(0.76, 0,83)
Barretos, Brazil	0.84	(0.83,0.90)

METHODS:

We developed Mirai[1], a mammography-based risk model designed: to predict risk at multiple timepoints, benefit from non-image risk factors, and achieve consistent performance across multiple devices. We validated Mirai using a total of 128,793 mammograms from 62,185 patients were collected across the seven sites[2]. We then developed Tempo[3], a multi-objective reinforcement learning-based framework for personalized screening, and validated its policies across datasets from four sites.

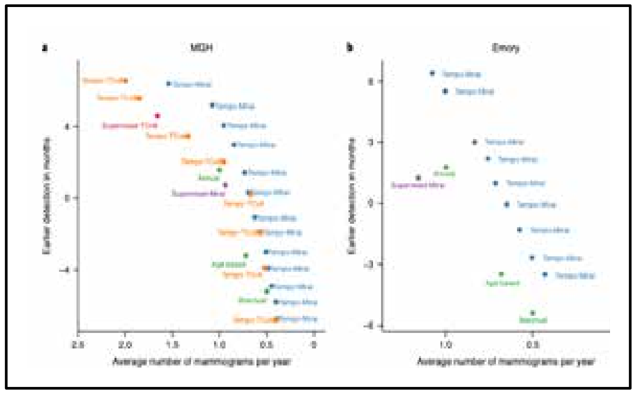


Figure 1. Performance of Tempo in improving screening efficiency in the MGH and Emory test sets.

RESULTS:

Mirai maintained its accuracy across globally diverse test sets from seven hospitals across five countries (Table 1). Tempo personalized screening policies consistently improved early detection while reducing overall screening in simulation studies across diverse populations (Figure 1).

CONCLUSION:

Machine learning methods for risk modeling and personalized screening can offer consistent and significant improvements over traditional approaches.

What is the key finding new since 2019?

AI tools for cancer risk and policy design are robust.

How does this finding impact screening strategies for women?

These findings motivate prospective studies for AI-driven personalized screening approaches.

REFERENCES:

1. Yala, Adam, et al. "Toward robust mammography-based models for breast cancer risk." *Science Translational Medicine* 13.578 (2021): eaba4373.
2. Yala, Adam, et al. "Multi-institutional validation of a mammography-based breast cancer risk model." *Journal of Clinical Oncology* 40.16 (2022): 1732-1740.
3. Yala, Adam, et al. "Optimizing risk-based breast cancer screening policies with reinforcement learning." *Nature medicine* 28.1 (2022): 136-143.

BEYOND MAMMOGRAPHIC DENSITY: NOVEL RADIOMIC PHENOTYPES AND 3D BREAST DENSITY MEASURES

[1]Kontos, Despina
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Despina.Kontos@pennmedicine.upenn.edu

INTRODUCTION:

Studies have repeatedly shown that breast density, which limits mammographic sensitivity, is also a strong risk factor for breast cancer. As a result, breast density information is increasingly utilized in guiding personalizing breast cancer screening and prevention. Conventional 2D mammography, however, is inherently limited due to the effect of tissue superimposition in estimating breast density. In addition, the commonly used measures of mammographic density cannot fully capture the heterogeneity of the breast parenchymal pattern, shown to be an important additional indicator of breast cancer risk.

OBJECTIVES:

Breast Tomosynthesis is an emerging 3D x-ray breast imaging modality, which offers superior, tomographic breast tissue visualization compared to conventional 2D mammography. Multiple studies have shown that screening with tomosynthesis reduces recalls while increasing cancer detection compared to screening with mammography alone, which is currently fueling a broad implementation of tomosynthesis for general population breast cancer screening. In addition to improved screening performance, our hypothesis is that 3D measures of breast density and parenchymal pattern complexity from breast tomosynthesis can outperform density measures from conventional 2D mammography, to improve breast cancer risk estimation.

METHODS:

This talk will review recent investigations in volumetric density estimation and parenchymal texture analysis in digital breast tomosynthesis[1-3]. We will also review preliminary evaluations on the association between these novel 3D measures of breast density and texture with breast cancer[4].

RESULTS:

We will review studies that have shown compelling early evidence that novel 3D measure of breast density and parenchymal complexity from breast tomosynthesis can provide powerful new imaging markers that can augment the standard mammographic density and texture measures in breast cancer risk estimation. Within this setting, we will also discuss the performance of measures derived from synthetic digital mammograms, increasingly replacing conventional digital mammography images in tomosynthesis acquisition.

CONCLUSION:

Growing studies suggest that further development in tomosynthesis imaging biomarkers is warranted to augment breast cancer risk assessment and provide the necessary tools to enable larger multi-center studies on breast cancer risk assessment.

REFERENCES:

1. Acciavatti RJ, Lee SH, Reig B, Moy L, Conant EF, Kontos D, Moon WK. Beyond Breast Density: Risk Measures for Breast Cancer in Multiple Imaging Modalities. Radiology. 2023 Mar; 306(3):e222575.

2. Gastounioti A, Pantalone L, Scott CG, Cohen EA, Wu FF, Winham SJ, Jensen MR, Maidment ADA, Vachon CM, Conant EF, Kontos D. Fully Automated Volumetric Breast Density Estimation from Digital Breast Tomosynthesis. Radiology. 2021 Dec;301(3):561-568.

3. Gastounioti A, McCarthy AM, Pantalone L, Synnestvedt M, Kontos D, Conant EF. Effect of Mammographic Screening Modality on Breast Density Assessment: Digital Mammography versus Digital Breast Tomosynthesis. Radiology. 2019 May;291(2):320-327.

4. Conant EF, Keller BM, Pantalone L, Gastounioti A, McDonald ES, Kontos D. Agreement between Breast Percentage Density Estimations from Standard-Dose versus Synthetic Digital Mammograms: Results from a Large Screening Cohort Using Automated Measures. Radiology. 2017 Jun;283(3):673-680.

Longitudinal analysis of density change in each breast assessed by digital mammograms is associated with breast cancer

[1]Jiang, Shu; [2]Bennett, Debbie; [3]Rosner, Bernard; [1]Colditz, Graham
[1]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, MO [2]Department of Radiology, Washington University School of Medicine, MO [3]Brigham and Women's Hospital, Boston, MA.

INTRODUCTION:

Although breast density is an established risk factor for breast cancer, longitudinal changes in breast density have not been extensively studied to determine whether this additional data point is associated with breast cancer risk. Specifically, no study has looked at the correlated bivariate breast density change in each breast and its association with breast cancer.

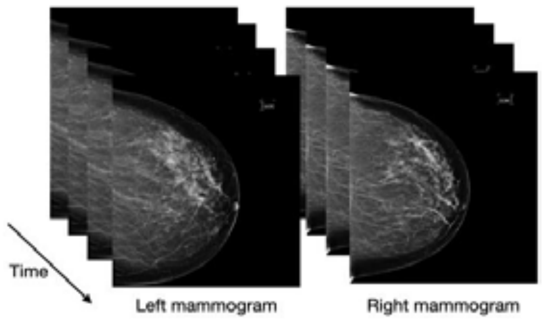

Figure 1. Illustration of the routinely available bivariate longitudinal screening mammogram data for each woman.

OBJECTIVES:

To prospectively evaluate the association between change in mammographic density in each breast over time and risk of subsequent breast cancer.

METHODS:

Design: This case-control study was sampled from the Joanne Knight Breast Health Cohort of 10,481 women free from cancer followed from 2008 to 2020 with routine screening mammograms every 1 to 2 years.
Setting: Breast screening service for diverse population of women in the St. Louis region.
Participants: 289 pathology-confirmed breast cancer cases were identified and approximately 2 controls were sampled for each case based on age at entry and year of enrollment giving 658 controls with a total number of 8,710 craniocaudal (CC) view mammograms for analysis.
Model: A correlated linear mixed effects model was used to model the bivariate longitudinal density for each woman.

RESULTS:

The mean age of participants was 56.6 years at entry; 81.3% were white. The mean interval was 2 years from time of last mammogram to date of subsequent breast cancer diagnosis (10^{th} percentile: 1.0, 90^{th} percentile: 3.9 years). Breast density decreased over time in both case and control groups of women. There was a significantly slower decrease in density over time in breasts that subsequently developed breast cancer (slope = -0.050 per year) compared to the rate of density change in control women (slope = -0.077 per year; P = 0.04).

CONCLUSION:

Rate of change in breast density is associated with risk of subsequent breast cancer. Incorporation of longitudinal changes into existing models could optimize risk stratification and guide more personalized risk management.

What is the key finding new since 2019?

Evaluating longitudinal changes in breast density from digital mammograms may offer an additional tool for assessing individual risk of breast cancer and subsequent risk reduction strategies.

How does this finding impact screening strategies for women?

These repeated measures can be further refined for routine practice and incorporated into dynamic risk classification and hence guide personalized prevention services according to the woman's individual level of risk.

REFERENCES:

1. Jiang, S.; Bennett, DL; Rosner, B.; Colditz, GA. Longitudinal analysis of density change in each breast assessed by digital mammograms is associated with breast cancer. *JAMA Oncology* 2023. In press.

ULTRASOUND IMAGING MARKERS OF BREAST CANCER RISK

[1]Duric, Neb
[1]University of Rochester, Rochester, NY (email: Nebojsa_Duric@urmc.rochester.edu)

INTRODUCTION:
The percentage of dense tissues in the breast, as measured by mammography, is a major cancer risk factor. At the same time, the sensitivity of mammography is inversely proportional to increasing breast density. Thus, the population of women that would benefit most from screening, get the least accurate mammograms. Furthermore, adding mammographic percent density (MPD) to clinical risk models improves predictive accuracy only modestly and not enough to provide individualized assessment, thereby limiting options for this population of women. Other imaging modalities could provide additional risk stratification but would require a separate exam from the general screening process (e.g. MRI). There is therefore a need for an imaging modality that improves risk prediction while also improving screening sensitivity. For dense breast imaging, where risk stratification would be most useful, we review the possible role of screening ultrasound (US).

OBJECTIVES:
In this review we discuss the current and future role of US for assessing breast density and risk assessment. We also present recent results from case control studies that examined baseline risk stratification and monitoring of risk prevention strategies.

METHODS:
We review the literature for US-based studies that include results from hand held ultrasound (HHUS), automated breast ultrasound (ABUS) and ultrasound tomography (UST). Areas of focus included (i) breast density measurements, (ii) generation of new risk factors and (iii) monitoring breast changes during risk reduction therapy.

RESULTS:
HHUS and ABUS have shown that background echogenicity is associated with breast density measures from mammography and MRI[1-2]. In a novel approach, HHUS, in combination with a mirror, has demonstrated the ability to measure speed of sound of the breast,[3] a quantitative measure that is directly proportional to physical tissue density. The emerging modality of UST images the uncompressed breast and the associated true 3D distributions of dense tissue, a potential advantage over conventional US. Studies with UST sound speed measurements indicate that volumetric speed of sound is strongly associated with both MPD and MR measures of breast density.[4-6]

In a case-control pilot study, UST has demonstrated an increase in risk stratification compared to MPD[7]. Furthermore, UST has also shown that breast sound speed changes during adjuvant treatment[8] (e.g. Tamoxifen) and that these changes are associated with changes in metabolite levels.

CONCLUSION:
ABUS and, more recently, UST, have been approved for dense breast screening. There is therefore an opportunity to examine their role in risk assessment during the breast cancer screening process.

What is the key finding new since 2019? US has the potential to improve risk stratification now made more feasible by the recent FDA approval of UST for dense breast screening.

How does this finding impact screening strategies for women? Simultaneously improving risk assessment and detection may lead to more personalized screening.

REFERENCES:
1. Chen, J.H., et al 2009. Breast density analysis for whole breast ultrasound images. *Medical physics*, 36, pp.4933-4943.
2. Moon, W.K., et al. 2010. Comparative study of density analysis using automated whole breast ultrasound and MRI. *Medical Physics*, 38(1), pp.382-389.
3. Ruby, L., et al 2019. Breast density assessment in young women with ultrasound based on speed of sound: influence of the menstrual cycle. *Medicin*e, 98(25).
4. Duric N, et al 2013. Breast density measurements with ultrasound tomography: a comparison with film and digital mammography. *Med Phys*, 40(1):013501
5. O'Flynn EAM, et al 2017. Ultrasound Tomography Evaluation of Breast Density: A Comparison With Noncontrast Magnetic Resonance Imaging. *Invest Radiol*. 52(6):343-8.
6. Wiskin J, et al. 2019. Quantitative assessment of breast density using transmission ultrasound tomography. Med Phys.46(6):
7. Duric N, et al. 2021 Using Whole Breast Ultrasound Tomography to Improve Breast Cancer Risk Assessment: A Novel Risk Factor Based on the Quantitative Tissue Property of Sound Speed. *J Clin Med., 9(2), p.367.*
8. Gierach, G.L., et al 2022. Rapid Reductions in Breast Density following Tamoxifen Therapy as Evaluated by Whole-Breast Ultrasound Tomography. *J Clin Med*, 11(3), p.792

Breakfast
7:00 AM - 8:00 AM - Ballroom 1+2

Sponsored by Volpara Health.

Housekeeping
8:00 AM - 8:10 AM - Ballroom 3+4

Breast Cancer Risk Assessment and Modeling
Moderator: Rulla Tamimi

8:10 AM - 9:05 AM - Ballroom 3+4

PLENARY TALK 7

Mammography Derived Risk Beyond Breast Density: Contribution of AI Models Combined with Mammographic Density on Breast Cancer Risk
Celine M. Vachon, PhD
Professor of Epidemiology and Consultant, Mayo Clinic

ABSTRACT PROFFERED TALK - POSTER #14

Breast Cancer Risk Assessment Improves by Combining Artificial Intelligence for Lesion Detection and Mammographic Texture-Based Risk
Andreas Lauritzen, Department of Computer Science, University of Copenhagen

Coffee Break
9:05 AM - 9:35 AM - Pre-Function Room

Breast Cancer Risk Assessment and Modeling (Continued)
9:35 AM - 11:25 AM - Ballroom 3+4

PLENARY TALK 8

Alternative Methods to Measure Breast Density in Younger Women
Jennifer Stone, PhD
A/Prof, University of Western Australia

PLENARY TALK 9

Risk Assessment for Digital Breast Tomosynthesis to Identify Women Who Need Additional Care
Mikael Eriksson, PhD
Department of Medical Epidemiology and Biostatistics
Karolinska Institutet
Sweden

ABSTRACT PROFFERED TALK - POSTER #49

Advancing Evidence of the Associations Between Specific Benign Breast Diagnoses and Future Breast Cancer Risk
Olivia Sattayapiwat, University of California, Davis

ABSTRACT PROFFERED TALK - POSTER #6

Glandular Tissue Component on Breast Ultrasound: A New Imaging Biomarker for Breast Cancer Risk
Woo Kyung Moon, Department of Radiology, Seoul National University Hospital

Lunch
11:25 AM - 12:25 PM - Ballroom 1+2

Breast Cancer Risk Assessment and Modeling (Continued)
Moderator: John Shepherd

12:25 PM - 1:20 PM - Ballroom 3+4

PLENARY TALK 10

Changes in Mammographic Density and Breast Cancer in a Population Enriched for Family History of Breast Cancer
Parisa Tehranifar, DrPH
Associate Professor, Epidemiology at Columbia University Irving Medical Center

ABSTRACT PROFFERED TALK - POSTER #46

Image-Based Models for Predicting Advanced Breast Cancer Risk
Arianna Bunnell, University of Hawaii Cancer Center

Poster Session 2 + Coffee Break

1:20 PM - 2:20 PM - Pre-Function Room

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Disparity and Underrepresented Populations

2:25 PM - 3:35 PM - Ballroom 3+4

ABSTRACT PROFFERED TALK - POSTER #4

Early Life Socioeconomic Status and Breast Tissue Composition in Adolescent Girls and Their Mothers
Rebecca Kehm, Columbia University

ABSTRACT PROFFERED TALK - POSTER #15

Effectiveness of Breast Density Educational Interventions on Mammography Screening Adherence Among Latinas: A Randomized Controlled Trial
Jessica Austin, Mayo Clinic Arizona

PLENARY TALK 11

High Mammographic Density in Black Women: Determinants and Association with Breast Cancer
Kimberly Bertrand, ScD
Associate Professor of Medicine Slone Epidemiology Center at Boston University

Panel Discussion and Questions

3:35 PM - 3:50 PM - Ballroom 3+4

Closing Remarks

3:50 PM - 4:00 PM - Ballroom 3+4

MAMMOGRAPHY DERIVED RISK BEYOND BREAST DENSITY: CONTRIBUTION OF AI MODELS COMBINED WITH MAMMOGRAPHIC DENSITY ON BREAST CANCER RISK

[1]Vachon, Celine M; [1]Scott CG; [2]Banerjee I; [1]Norman AD, [1]Hursh D, [1]Jensen MR, [1]Brandt KR, [1]Winham SJ, [3]Kerlikowske K
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INTRODUCTION:
AI models based on deep learning have been developed for lesion detection and diagnosis in mammography as well as for breast cancer risk. There are limited data, however, for the performance of these AI models in predicting long term risk of invasive cancer and risk of advanced and interval cancers, as well as how they contribute to breast density and other clinical measures.

OBJECTIVES:
We evaluate the contribution of two AI models (Transpara AI cancer detection system and Mirai 5-year risk) combined with volumetric density measures to overall invasive, interval, screen-detected, advanced, and non-advanced cancer risk. We hypothesize that both the AI Transpara score and Mirai 5-year risk, will improve long-term risk prediction of invasive, interval and advanced cancer above volumetric density measures.

METHODS:
We conducted a case-control study of 2,412 women with invasive breast cancer (cases) and 4,995 women without breast cancer (controls) matched on age, race, date of mammogram and machine, nested within two large US-based breast screening practices, the San Francisco Mammography Registry (SFMR) and the Mayo Clinic, Rochester (Mayo). Women having screening full-field digital mammography between 2007-2017 (SFMR) or 2009-2017 (Mayo) without prior history of breast cancer were eligible.

Cancer endpoints at least six months after screening mammogram were identified through state and clinic tumor registries. We classified invasive breast cancer as interval (within 12 months of negative screening mammography), screen-detected (within 12 months of positive screening mammography), advanced (AJCC pathologic stage II or higher) and non-advanced cancer. Primary analyses restricted to invasive cases only and mammograms between 2 and 5.5 years before diagnosis or last follow-up.

We estimated the Transpara AI malignancy score (1-10) and Volpara volumetric density measures on mammograms from both studies and 5-year Mirai risk on the Mayo study only (824 cases/2,234 controls). We used conditional logistic regression to estimate odds ratios (ORs), 95% CIs, adjusted for age and BMI, and C-statistics (AUC) to describe the association of AI score with invasive cancer and its contribution to models with breast density measures. Likelihood ratio tests (LRTs) and bootstrapping methods were used to compare model performance.

RESULTS:
On mammograms 2-5.5 years prior to cancer, Transpara score (OR=1.20, 95% CI, 1.17 to 1.22 per one unit increase) and Mirai risk (OR=1.63, 95% CI, 1.50 to 1.77 per one standard deviation log Mirai) were associated with increased invasive breast cancer. Both AI models were predictive of interval and advanced cancers and in dense breasts.

The addition of Transpara AI score improved prediction of all cancer types in models with density measures (P_{LRT} values<.001); discrimination improved for advanced cancer (i.e., AUC for dense volume (DV) increased from 0.624 to 0.679, ΔAUC=0.065, P< .01) but did not reach statistical significance for interval cancer (i.e., AUC for DV increased 0.646 to 0.694, ΔAUC=0.043, P=0.09). The contribution of Mirai 5-year risk to models with density measures will be presented.

CONCLUSION:
AI models coupled with breast density measures contribute to long-term risk prediction of invasive breast cancers.

What is the key finding new since 2019?
AI models for risk and detection contribute new information for risk prediction of invasive breast cancers combined with breast density measures.

How does this finding impact screening strategies for women?
Both breast density and AI scores will be important for accurate prediction of invasive cancer outcomes, in particular advanced cancer.

ALTERNATIVE METHODS TO MEASURE BREAST DENSITY IN YOUNGER WOMEN

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INTRODUCTION

Breast density is a strong and potentially modifiable breast cancer risk factor. Almost everything we know about breast density has been derived from mammography, and therefore, very little is known about breast density in younger women aged <40.

OBJECTIVES: This study examines the acceptability and performance of two alternative breast density measures, Optical Breast Spectroscopy (OBS) and Dual X-ray Absorptiometry (DXA), in women aged 18-40.

Figure 1. OBS cups and device. Photo demonstrating the four OBS cup sizes in the top photo and the OBS device in use on a participant in the bottom photo

METHODS: Breast tissue composition (percent water, collagen, and lipid content) was measured in 539 women aged 18-40 using OBS. For a subset of 169 women, breast density was also measured via DXA (percent fibroglandular dense volume (%FGV), absolute dense volume (FGV), and non-dense volume (NFGV)). Acceptability of the measurement procedures was assessed using an adapted validated questionnaire. Performance was assessed by examining correlation and agreement between the measures and their associations with known determinants of mammographic breast density.

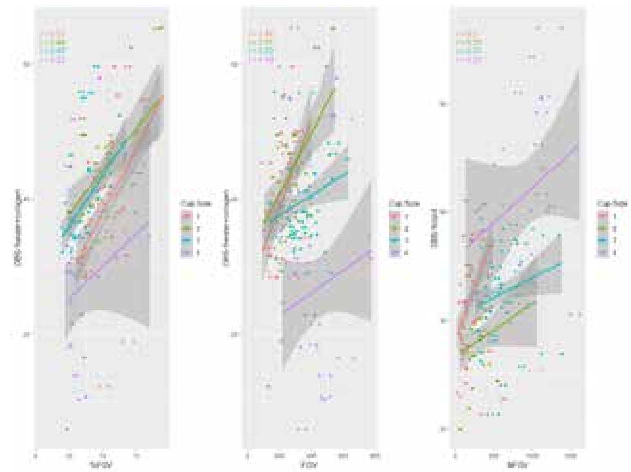

Figure 2. Correlations of OBS and DXA measures. Correlations (r) and scatterplots of DXA breast density measures (x axis) and OBS breast density measures (y axis), stratified by cup size (1-red; 2-green; 3-blue; 4-purple) for the 132 women who had both OBS and DXA scans. Panel 1: %FGV vs OBS-%water+collagen; Panel 2: FGV and OBS-%water+collagen; Panel 3: NFGV and OBS-%lipid

RESULTS: Over 93% of participants deemed OBS and DXA to be acceptable. The correlation between OBS-%water+collagen and %FGV was 0.48. Age and BMI were inversely associated with OBS-%water+collagen and %FGV and positively associated with OBS-%lipid and NFGV.

CONCLUSION: OBS and DXA provide acceptable and viable alternative methods to measure breast density in younger women aged 18-40 years.

What is the key finding new since 2019? This study provides new evidence regarding the determinants of breast density in younger women, suggesting that much of what we know about the factors that influence breast density in older women can be extrapolated to younger women.

How does this finding impact screening strategies for women? These findings have important implications for future research investigating the utility of measuring breast density in younger women to identify and target those at increased risk of breast cancer later in life.

RISK ASSESSMENT FOR DIGITAL BREAST TOMOSYNTHESIS TO IDENTIFY WOMEN WHO NEED ADDITIONAL CARE

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INTRODUCTION:

In clinical practice, many women who are at high risk of breast cancer are not adequately identified for more intensive or supplemental screening and present with breast cancer either prior to or at their next routine screen. Screening in the U.S. is commonly performed using Digital Breast Tomosynthesis (DBT). Supplemental screening is offered at hospitals, but models for selecting women for such additional screening have low to moderate accuracy. No breast cancer risk model has taken advantage of the additional information generated by DBT imaging for breast cancer risk prediction.

OBJECTIVES:

To develop and validate an image-based risk model using AI to leverage the risk information generated in DBT screening.

To identify women who need additional care after a negative mammogram for the earlier detection of breast cancer.

METHODS:

We studied a screening population of 154,200 women in age 35-74 who attended DBT screening at four screening units in U.S. between 2014-2019. After 1 year of follow-up, we included the available 805 incident breast cancers and a random sample of 5,173 healthy women matched on year of study-entry in a nested case-control study.
A model for predicting breast cancer risk was trained using elastic-net logistic regression and nested cross-validation to estimate risks for artificial intelligence derived imaging features (density, microcalcifications, masses, asymmetries) and age. An absolute risk model was developed using derived risks and U.S. incidence and competing mortality rates. Absolute risks, discrimination performance, calibration, and risk stratification were estimated in the independent validation set.
Absolute risks were classified using USPSTF and NICE guidelines for defining high, moderate, general, and low risk. The risk category indicates the clinical follow-up strategy for the woman.
The ability of the model to identify women with later stage breast cancer was reported.

RESULTS:

The discrimination performance of the 1-year risk model was 0.82 (95%CI 0.79-0.85) with good model-calibration (p=0.7). Using the U.S. Preventive Service Task Force USPSTF guidelines, 14% of the women were at high risk with 19.6 times higher risk compared to the general risk population.

Table 1: Discriminatory performance for DBT

	AUC	95% CI
Vendors combined	0.82	0.79 - 0.85
Hologic	0.88	0.85 - 0.91
Siemens	0.76	0.69 - 0.82
GE	0.77	0.66 - 0.86

Table 2: Risk classification using USPSTF

Risk group	Women at risk	Risk ratio
General	45	1.0 (ref.)
Moderate	41	5.2
High	14	19.6

In the high-risk group, 76% of stage II and III cancers and 59% of stage 0 cancers were observed, p<0.01. Similar predictive performances were observed in women with dense and non-dense breasts.

CONCLUSION:

The short-term DBT risk model has the potential to guide clinicians in selecting women for additional care, potentially leading to earlier detection and improved prognoses.

What is the key finding new since 2019?

DBT risk is now under evaluation at some clinics in the U.S. Further work is performed to generalize the results across different screening settings.

How does this finding impact screening strategies for women?

Clinicians and researchers are working to form a clinical protocol to identify women who need additional care after a negative screen.

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Changes in Mammographic Density and Breast Cancer in a Population Enriched for Family History of Breast Cancer

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INTRODUCTION:

Increasing mammographic density (MD) or remaining at a high MD over time may be more informative for breast cancer (BC) risk than a single measure of MD.[1] It is unclear whether the association of longitudinal MD change (MDC) patterns with BC risk differs with baseline MD, age or menopausal status, and extent of BC family history. Such information is essential for informing clinical translation and interpretation of MDC.

OBJECTIVES: to assess the association of greatest MDC between any two mammograms with BC risk, by baseline MD, BC family history, and menopausal status in a population enriched for BC family history.

METHODS: We conducted a nested case-control study within the prospective Sister Study cohort of BC-free U.S. women, >96% of whom had at least one sister with BC. 323 cases and 899 controls provided ≥ 2 cranio-caudal (CC) same-side mammograms ≥ 9 months apart, at ≤ age 60. We used Cumulus to calculate dense area (DA, cm^2) and percent density (PD, dense area/total breast area * 100). We categorized largest relative annual MDC as decreased (>10%), stable (+/-≤10% change) or increased (>10%) for PD and DA. We used logistic regression models adjusting for earlier MD, baseline body mass index (BMI), number of 1st or 2nd degree relatives with BC, and age at earlier mammogram.

RESULTS:

Compared to decreasing MD over time, women with stable MD had increased BC risk (e.g., OR 1.93 (1.39-2.69) for PD OR 2.34 (1.63-3.37) for DA). Within the highest tertile of DA, stable or increasing DA were both associated with risk. This was not seen among those in lower tertiles (**Table 1**). Although stronger associations were observed for pre-menopausal MDC in DA, patterns of increasing BC risk with stable DA were similar by menopausal status. Compared to having one relative with BC and decreasing MD, women with more relatives with BC had a higher BC risk regardless of MDC, with the strongest estimates observed for women with stable MD and ≥ 3 relatives with BC **(Fig. 1)**.

CONCLUSION: Stable or increasing MD in women with high MD confers greater BC risk than decreasing MD with similar patterns by menopausal status and extent of family history.

What is the key finding new since 2019? Using longitudinal mammograms to determine largest MDC, stable but high MD is associated with BC risk regardless of BC family history or menopausal timing of the largest MDC, supporting greater surveillance of women whose MD stays high.

Table 1. Associations of largest annual relative change in PD and DA with BC, by tertile of earlier MD (n=1222 women)

Relative change	Lowest tertile OR (95% CI)	Middle tertile OR (95% CI)	Highest tertile OR (95% CI)	MDC*MD P-value
PD Decreased	Ref	Ref	Ref	0.62
PD Stable	1.22 (0.55-2.72)	**1.82 (1.04-3.16)**	**2.14 (1.40-3.58)**	
PD Increased	0.87 (0.45-1.70)	1.09 (0.62-1.92)	0.87 (0.49-1.56)	
DA Decreased	Ref	Ref	Ref	0.02
DA Stable	1.14 (0.52-2.52)	1.58 (0.84-2.96)	**4.35 (2.53-7.50)**	
DA Increased	1.15 (0.61-2.18)	0.99 (0.57-1.73)	**2.56 (1.50-4.36)**	

Adjusted for age and MD at earlier mammogram, BC family history, BMI at baseline, and change*earlier MD interaction.

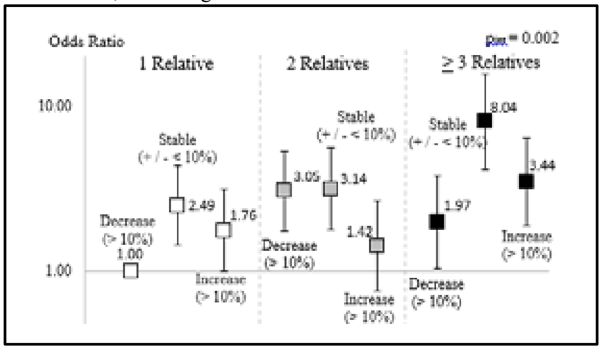

Figure. 1. Largest relative MDC in DA by BC family history.

How does this finding impact screening strategies for women? Women with family history of breast cancer who remain at high MD over time may be at increased BC risk and may benefit from frequent mammography and additional screening modalities.

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HIGH MAMMOGRAPHIC DENSITY IN BLACK WOMEN: DETERMINANTS AND ASSOCIATION WITH BREAST CANCER

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INTRODUCTION:

While high mammographic density (MD) is considered an established risk factor for breast cancer, relatively few prior studies have reported estimates of associations among Black women, who have higher incidence of aggressive subtypes and greater overall mortality from breast cancer compared to women of other racial/ethnic groups. Further, few prior studies have reported predictors of MD specifically in Black women, even though Black women may have greater MD (measured quantitatively) than white women.

OBJECTIVES:

1. To evaluate associations of MD with risk of breast cancer, overall and by subtype, in Black women.
2. To determine reproductive and lifestyle predictors of high MD in Black women.

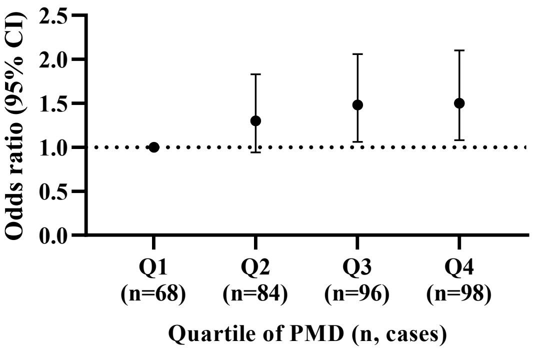
METHODS:

We established a case-cohort study within the Black Women's Health Study, a prospective U.S. cohort of self-identified Black women that began in 1995. We collected digital screening (pre-diagnostic) mammograms from 5,904 women (346 cases, 5558 non-cases) ages 40-74 at the time of mammography. We assessed percent MD (PMD) using Cumulus. We fit unconditional logistic regression models, adjusted for age and body mass index (BMI) at the time of mammography, to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer per quartile of PMD, overall and stratified by age (<55, ≥55 years). In addition, we used linear regression to quantify associations of reproductive and lifestyle factors (assessed on follow-up questionnaires), adjusted for age and BMI at mammogram, with PMD as the dependent variable.

RESULTS:

The average age at mammogram for both cases and non-cases was 56 years. Mean PMD was 26.3% among cases and 24.5% among non-cases. Women in the top quartile of PMD had 50% higher odds of breast cancer compared to those in the bottom quartile (OR: 1.50; 95% CI: 1.08, 2.10; p-trend <0.01) (Figure 1). Results were somewhat stronger for women ages 55 and older.

Figure 1. Association of PMD and breast cancer



Among women ages <55 years, compared to nulliparous women, those with 3 or more births had a 1.6 percentage point higher mean PMD (95% CI: 0.03, 3.1; p-trend <0.01). Other reproductive factors (age at menarche, age at first birth, age at last birth, lactation history) and lifestyle factors (oral contraceptive use, smoking history, alcohol consumption) were not significantly associated with PMD in either younger or older Black women.

CONCLUSION:

Consistent with findings in white women, Black women with greater PMD had increased risk of developing breast cancer. Analyses are ongoing to evaluate associations of PMD with risk of breast cancer defined by estrogen receptor status.

What is the key finding new since 2019?

Recent studies in Black women considered subjective measures of MD;[1,2] this study extends the literature by reporting on breast cancer associations with quantitative measures of MD.

How does this finding impact screening strategies for women?

These findings will be used to build better breast cancer risk prediction models for Black women.

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1. Bissell MCS et al. Breast Cancer Population Attributable Risk Proportions Associated with Body Mass Index and Breast Density by Race/Ethnicity and Menopausal Status. *Cancer Epidemiol Biomarkers Prev.* 2020
2. Friebel-Klingner et al. Risk factors for breast cancer subtypes among Black women undergoing screening mammography. *Breast Cancer Res Treat.* 2021

2. **Risk of Onset Versus Risk of Diagnosis: Using Modeling to Clarify the Link Between Breast Density and Cancer Risk in the Presence of the Masking Effect**
   Jane Lange, Center for Early Detection Advanced Research, Knight Cancer Institute, Oregon Health and Sciences University
4. **Early Life Socioeconomic Status and Breast Tissue Composition in Adolescent Girls and Their Mothers**
   Rebecca Kehm, Columbia University
6. **Glandular Tissue Component on Breast Ultrasound: A New Imaging Biomarker for Breast Cancer Risk**
   Woo Kyung Moon, Department of Radiology, Seoul National University Hospital
8. **Interim Results from ScreenTrustMRI - A Randomized Clinical Trial Using a Combination of AI Models as a Selection Tool for Supplemental MRI**
   Fredrik Strand, Karolinska Institutet
10. **Reproducibility of Volumetric Fibroglandular Fraction in Dedicated Cone-Beam Breast CT**
   Srinivasan Vedantham, Department of Medical Imaging, University of Arizona
12. **Associations of Stem Cell Markers CD44, CD24, and ALDH1A1 in Benign Breast Biopsies with Mammographic Breast Density**
   Rulla Tamimi, Weill Cornell Medicine
14. **Breast Cancer Risk Assessment Improves by Combining Artificial Intelligence for Lesion Detection and Mammographic Texture-Based Risk**
   Andreas Lauritzen, Department of Computer Science, University of Copenhagen
16. **Risk Perceptions and Mammography Screening Behavior Among Underserved, Hispanic Women: Implications for Risk-Based Screening**
   Jessica Austin, Mayo Clinic Arizona
18. **Predicting Breast Cancer with MRI for Individual Risk-Adjusted Screening and Early Detection**
   Lukas Hirsch, City College of New York
20. **Alcohol Consumption During Adolescence Modifies the Composition of the Breast**
   Ana Pereira, Universidad de Chile
22. **Unravelling the Contribution of Risk, Masking and Cancer Signs Models to the Selection of Women for Supplemental Imaging in the Prospective ScreenTrustMRI Trial**
   Mattie Salim, karolinska institute, department of oncology and pathology
24. **Association Between Premenopausal Breast Density and Body Composition**
   Holly Harris, Public Health Sciences, Fred Hutch Cancer Center
26. **Volumetric Parenchymal Pattern Analysis for Breast Cancer Risk Estimation**
   Alex Nguyen, University of Pennsylvania Perelman School of Medicine
28. **Elevated Numbers of Terminal Duct Lobular Units in the Normal Breast are Associated with Inflammation and a Unique Immune Landscape**
   Brittany Lord, Division of Cancer Epidemiology and Genetics, National Cancer Institute
30. **Relationships Between Automated Volumetric Local and Global Breast Density Assessments Among Women Undergoing Diagnostic Image-Guided Breast Biopsy**
   Shaoqi Fan, National Cancer Insitute
32. **Stromal Disruption on Histologic Sections Impairs Tamoxifen-Associated Mammographic Density Reduction and Portends Poor Prognosis in Estrogen Receptor-Positive Breast Cancer**
   Mustapha Abubakar, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health
34. **Longitudinal Mammographic Breast Percent Density Changes for Breast Cancer Risk Estimation: Proof-of-Concept Study**
   Juhun Lee, University of Pittsburgh
36. **Causal Relationships Between Mammogram Risk Scores Based on Textural Features and Density**
   Zhoufeng Ye, The University Of Melbourne
38. **Multiscale Anisotropy Analysis Of Second-Harmonic Generation Images of Breast Tissue Microenvironment**
   Joshua Hamilton, University of Maine, Graduate School of Biomedical Science and Engineering
40. **Amino Acid Metabolites and Mammographic Breast Density in Premenopausal Women**
   Kayla Getz, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine in St. Louis
42. **Assessing Improvements in Dense Tissue Visualization in Next-Generation Tomosynthesis Through Mastectomy Specimen Imaging**
   Andrew Maidment, Perelman School of Medicine at the University of Pennsylvania
44. **Characterizing the Effects of Anti-Inflammatory Drug Sulindac on the Extracellular Matrix Proteins of Breast Tissue**
   Patricia Thompson, Cedars-Sinai Medical Center
46. **Image-Based Models for Predicting Advanced Breast Cancer Risk**
   Arianna Bunnell, University of Hawaii Cancer Center
48. **Predicting Lesion Masking Risk in Mammograms in the Dutch National Breast Cancer Screening Program**
   Sarah Verboom, Radboud University Medical Center, Department of Medical Imaging
50. **Interval Cancer Predictors Beyond A, B, C, D**
   Melissa Hill, Volpara Health
52. **The Hawaii and Pacific Islands Mammography Registry**
   Dustin Valdez, University of Hawaii Cancer Center

Poster Session 2 | Friday, June 9, 2023

1. **The Benefits and Harms of Risk-Reducing Medication and Screening in High-Risk Women: A Simulation Modeling Study**
   Jinani Jayasekera, National Institutes of Health/National Institute on Minority Health and Health Disparities

3. **Women's Responses to Breast Density Notifications vary by Literacy and Sociodemographic Characteristics**
   Christine Gunn, The Dartmouth Institute for Health Policy and Clinical Practice

5. **Supplemental Breast Cancer Screening After Negative Mammography in U.S. Women with Dense Breasts**
   Amy Trentham-Dietz, University of Wisconsin-Madison

7. **Communicating Risk via a Breast Cancer Screening Decision aid for Women in their 40s with Limited Health Literacy**
   Christine Gunn, The Dartmouth Institute for Health Policy and Clinical Practice

9. **Association of Breast Cancer with a Fully-Automated Measure of Background Parenchymal Enhancement**
   Gordon Watt, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center

11. **Harmonization of Site Effects in Image-Derived Features for Multicenter Mammography Studies**
    Hannah Horng, University of Pennsylvania

13. **Polygenic Score Predicts Early Onset Triple-Negative Breast Cancer in Black Women**
    Holly Pederson, Cleveland Clinic

15. **Effectiveness of Breast Density Educational Interventions on Mammography Screening Adherence Among Latinas: A Randomized Controlled Trial**
    Jessica Austin, Mayo Clinic Arizona

17. **Artificial Intelligence for Image-Based Breast Cancer Risk Prediction Using Attention**
    Stepan Romanov, University of Manchester

19. **Ultrasound Tomography Measures of Breast Density Decline by Treatment-Associated Endocrine Symptoms After Tamoxifen Therapy: Exploring the Role of CYP2D6 Phenotype and Tamoxifen Metabolites**
    Cody Ramin, National Cancer Institute and Cedars-Sinai Medical Center

21. **Feasibility of Quantitative Breast Density Measurements in Obese Women with Dedicated Cone-Beam Breast CT**
    Srinivasan Vedantham, Department of Medical Imaging, University of Arizona

23. **Current Measures of Mammographic Density are more Strongly Associated with Breast Cancer Risk in Asian Post-Menopausal Compared to Pre-Menopausal Women**
    Weang-Kee Ho, University of Nottingham

25. **Longitudinal Assessment of Active and Passive Dense Mammographic Tissue**
    Kendra Batchelder, University of Maine

27. **Growth and Development Factors Related to Mammographic Density in Black Women**
    Zahna Bigham, Tufts University Graduate School of Biomedical Sciences; Tufts Medical Center; Tufts University School of Medicine

29. **Characterizing the Immune Microenvironment in Benign and Cancerous Breast Biopsy Tissues in Relation to Mammographic Density**
    Alexandra Harris, National Cancer Institute

31. **Volumetric Breast Density: 2D vs 3D Methods**
    James Wiskin, QT Imaging, Inc.

33. **Relation of Pre- And Post-Diagnosis Measures of Mammographic Breast Density with Contralateral Breast Cancer Risk Among Breast Cancer Survivors**
    Gretchen Gierach, National Cancer Institute/Integrative Tumor Epidemiology Branch

35. **Mammographic Density and Breast Cancer-Specific Survival in the Breast Cancer Association Consortium**
    Gretchen Gierach, National Cancer Institute/Integrative Tumor Epidemiology Branch

37. **Examining Associations of Breast Cancer Risk Factors with Volumetric Measures of Breast Density at Increasing Thresholds Among Women Undergoing Diagnostic Image Guided Breast Biopsy**
    Maeve Mullooly, RCSI University of Medicine and Health Sciences

39. **Extending the Breast Cancer Surveillance Consortium Model (BCSC) of Invasive Breast Cancer**
    Jeff Tice, UCSF

41. **Addressing Class Imbalance and Overconfidence of U-Net Segmentation Models for Density and Risk Assessment**
    Andrew Maidment, University of Pennsylvania

43. **Interplay Between Genetic and Non-Genetic Factors Influencing Mammographic Density**
    Tabitha Harrison, University of Washington

45. **3D Ultrasound Tomography Volumetric Breast Density: Comparison of Methods**
    James Wiskin, QT Imaging Inc

47. **Artificial Intelligence Predicts Mammographic Breast Density from Clinical Breast Ultrasound Images**
    Arianna Bunnell, University of Hawaii Cancer Center

49. **Advancing Evidence of the Associations Between Specific Benign Breast Diagnoses and Future Breast Cancer Risk**
    Olivia Sattayapiwat, University of California, Davis

51. **An Analysis of High Performing Instagram Posts Targeted at Cancer Survivors**
    Joanne Hayashi, Breast Cancer Hawaii

THE BENEFITS AND HARMS OF RISK-REDUCING MEDICATION AND SCREENING IN HIGH-RISK WOMEN: A SIMULATION MODELING STUDY

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INTRODUCTION:

Recent studies show high rates of breast cancer recurrence and death in hormone-receptor positive early-stage breast cancer. These new findings suggest a need to evaluate the harms and benefits of risk-reducing medication and mammography screening in high-risk women.

OBJECTIVES: To provide the benefits and harms of risk-reducing medication, screening, and supplemental magnetic resonance imaging (MRI) to facilitate shared decision-making about risk-reducing drugs with high-risk women.

METHODS: We used an established Cancer Intervention and Surveillance Modeling Network (CISNET) model to evaluate the lifetime benefits and harms of risk-reducing medication in women with a ≥3% five-year risk of developing breast cancer according to the Breast Cancer Surveillance Consortium (BCSC)-risk calculator.[1] Model input parameters were developed from meta-analyses, large observational (BCSC and SEER data), and clinical trial data. We evaluated the effects of 5-years of risk-reducing medication (tamoxifen/aromatase inhibitors) with annual screening mammography± MRI compared to no screening, MRI, or risk-reducing medication. The modeled outcomes included invasive breast cancer, breast cancer death, side-effects and false positives. We conducted subgroup analyses for individual risk factors such as age, family history, and history of breast biopsy.

RESULTS: Risk-reducing medication (tamoxifen) with annual screening (+/-MRI) decreased the risk of invasive breast cancer by 40% and breast cancer death by 57%, compared to no tamoxifen or screening or MRI (Table 1). However, tamoxifen could increase the risk of cardiovascular events and endometrial cancers in high-risk women. Benefits and harms vary by individual risk factors.

Table 1: Benefits and Harms of Risk-Reducing Medication, Screening Mammography, and Supplemental Screening with Magnetic Resonance Imaging in High-Risk Women

Strategy	Benefits				Harms				
	No. of Invasive Breast Cancers* per 1000 High-risk Women	Percentage of Invasive Breast Cancers* Avoided[1]	No. of Breast Cancer Deaths per 1000 High-risk Women	Percentage of Breast Cancer Deaths Avoided[2]	Number of Adverse Events per 1000 High-risk Women				False Positive Results Per 1000 High-risk Women
					Venous Thromboembolism	DVT; PE; SP; CHD	Stroke	Endometrial cancer	
Annual S	201	15	45	39	-	-	-	-	1002
Annual S + R	142	40	32	57	5	2; 3; 2; <1	2	11	1054
Annual S + MRI	199	16	44	40	-	-	-	-	1823
Annual S + MRI + R	141	40	31	58	5	2; 3; 2; <1	2	11	1918
No S or MRI or R	237	-	74	-					-

S, annual screening mammography with digital breast tomosynthesis till age 74; R, 5-years of risk-reducing medication; DVT, deep vein thrombosis; PE, pulmonary embolism; SP, superficial phlebitis; CHD, Coronary Heart Disease; MRI, magnetic resonance imaging

*Includes both estrogen-receptor positive and negative breast cancer.

[1][(Difference between the number of invasive breast cancer cases among women who underwent a given strategy and women who did not undergo screening or MRI or risk-reducing medication)/ the number of invasive breast cancer cases among women who did not undergo screening, MRI, or risk-reducing medication] *100.

[2][(Difference between the number of breast cancer deaths in women who underwent a given screening strategy and women who did not undergo screening or risk-reducing medication)/ the number of breast cancer deaths in women who did not undergo screening, MRI, or risk-reducing medication] *100.

CONCLUSION: The addition of risk-reducing medication to screening and MRI could further decrease the risk of breast cancer death. However, these drugs are associated with side-effects such as stroke and endometrial cancer. The lifetime benefits and harms of risk-reducing drugs could vary based on age, prior biopsy, and family.

What is the key finding new since 2019?

Risk-reducing medication could decrease the risk of breast cancer death in high-risk women.

How does this finding impact screening strategies for women?

These findings could support shared-decision making regarding risk-reducing medication and mammography screening considering individual risk-factors in high-risk women.

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RISK OF ONSET VERSUS RISK OF DIAGNOSIS: USING MODELING TO CLARIFY THE LINK BETWEEN BREAST DENSITY AND CANCER RISK IN THE PRESENCE OF THE MASKING EFFECT

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INTRODUCTION:

Studies have shown that women with dense breasts have a higher risk of breast cancer diagnosis. This has impacted risk prediction tools and patient notification policies. Given that mammography is less sensitive for women with dense breasts (i.e., the *masking effect)* and these women may be subject to different confirmation testing pathways, the true association between breast density and breast cancer risk is unknown

OBJECTIVES:

Our goal was to use a natural history modeling approach to estimate the association between dense breasts and breast cancer onset in the Breast Cancer Surveillance Consortium (BCSC), accounting for differential mammography sensitivity and utilization patterns.

METHODS:

BCSC subjects included women with a first digital mammogram between 2000-2018 (N=33,542). Of these, 15,092 had non-dense (BIRADS I- II) and18,450 had dense (BIRADS III-IV) breasts. We approximated mammography sensitivity in women with dense and non-dense breasts estimated mammography rates and biopsy frequencies following a positive mammogram in each group. In conclusion, the association between breast density and the risk of developing breast cancer is similar to the association between breast density and the risk of breast cancer diagnosis and is robust against different values of mammography sensitivity in dense versus non-dense breasts.

RESULTS:

Sensitivity was 0.88 in women with non-dense and 0.78 in women with dense breasts. Mammograms were more frequent in women with dense breasts (Hazard ratio (HR) for time to next screen 1.10 (95% CI [1.07, 1.12]). The relative risk of diagnosis for dense versus non-dense breasts over five years was 1.8 (95% CI [1.46,2.57]); the relative risk of onset over a similar interval was 1.7 [1.43,2.25].
The relative risk of onset ranged from 1.67 to 2.03 as we varied the relative sensitivity for dense versus non-dense breasts between 1.0 to 0.4.

CONCLUSION:

The association between breast density and the risk of developing breast cancer is similar to the association between breast density and the risk of breast cancer diagnosis and is robust against different values of mammography sensitivity in dense versus non-dense breasts.

What is the key finding new since 2019?

This work uses a novel modeling approach to clarify longstanding questions about the relationship between breast density and breast cancer risk given that dense breasts are associated with lower mammography sensitivity.

How does this finding impact screening strategies for women?

Our approach enables more accurate breast cancer risk calculators that include breast density as a risk factor. We found that relative to non-dense (BI-RADs A,B), dense (BI-RADS C,D) breasts had about 1.7 times the risk of breast cancer onset within 5 years after the first screen. These results support existing screening recommendations for women with dense breasts.

Women's Responses to Breast Density Notifications Vary by Literacy and Sociodemographic Characteristics

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INTRODUCTION:

Legislation to require informing women of their breast density (BD) has been enacted in 38 US states and the District of Columbia; the U.S. Food and Drug Administration is preparing a nationwide notification. BD notifications aim to inform women of BD risks and encourage them to discuss personal risk and need for supplemental screening with their healthcare providers.

OBJECTIVES:

To understand women's preferences for and experiences learning about BD, as well as outcomes after BD notifications including knowledge, anxiety, confusion, feeling informed and future mammography plans, and whether these varied by race/ethnicity or literacy

METHODS:

1) National telephone survey of 2,306 racially/ethnically and literacy-level diverse women; qualitative interviews with 61 survey respondents.
2) Bivariate and multivariable analyses examined participant responses by race/ethnicity and literacy.
3) Content analysis generated interview themes.

RESULTS:

- Most women prefer to learn of BD from their healthcare provider but women with low literacy prefer written notification; women in BD notification states more often received personal BD information.
- Knowledge about BD is greater among white, more educated women with higher incomes, with numerous misunderstandings of BD in all racial/ethnic groups. Latinas and women with less literacy have less understanding about BD's masking effects. Less than half of all women realized that BD increases the risk of breast cancer.
- After being notified about BD, most women felt informed, but non-Hispanic Black women and women with less literacy or lower incomes were more likely to report anxiety and confusion. Some women reported that knowing their breast density changed their plans for future mammograms.

Few women reported having conversations with their providers to discuss personal risk and need for supplemental screening; but women in BD notification states were more likely.

CONCLUSION:

Differential reactions to BD information point to potential limitations of current BD notifications. Future notifications and BD education efforts should ensure that such information is readily accessible and understandable to all women, and leads to desired effects.

What is the key finding new since 2019?

Women prefer to learn of BD from their providers; there are numerous racial/ethnic and literacy-level disparities in outcomes after BD notifications, including changes in plans for future mammograms.

How does this finding impact screening strategies for women?

These results illustrate the importance of well-tested and carefully designed BD informational materials in equitably educating all women about screening, to ensure desired outcomes and minimize unintended outcomes.

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Early life socioeconomic status and breast tissue composition in adolescent girls and their mothers

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INTRODUCTION: Higher early life socioeconomic status (SES) is associated with increased breast cancer risk.[1] It is not known if this association is driven by changes to breast tissue composition (BTC) early in life, given that no study has evaluated SES and BTC prior to middle age.

OBJECTIVES: To determine if early life SES is associated with BTC in nulliparous adolescent girls. We also examined early life SES and BTC in adult parous women (the mothers of girls).

METHODS: We used data from a NYC cohort of nulliparous Black and Hispanic girls (n=165, 11-20 years), prospectively followed since birth, and their mothers (n=158, 29-55 years). We used optical spectroscopy to obtain measures of BTC that positively (% water, % collagen, optical index) and negatively (% lipid) correlate with mammographic density,[2] a recognized breast cancer risk factor.[3] We measured early life SES in girls using prospectively collected data on household income and maternal education at birth, analyzed separately and combined (SES index). We measured early life SES in women using retrospectively collected data on maternal education in infancy. We used multivariable linear regression models to evaluate associations overall and stratified by body mass index (BMI).

RESULTS: Being in the highest vs. lowest category of the early life SES index was associated with lower lipid content ($\beta_{adjusted}$ = -0.80, 95% CI = -1.29, -0.32) and higher collagen content ($\beta_{adjusted}$ = 0.58, 95% CI = 0.13, 1.03) in the breast tissue of adolescent girls. Associations did not differ between girls with a BMI < 25 kg/m^2 and a BMI ≥ 25 kg/m^2 (**Table 1**). Higher early life SES, as indicated by higher maternal education in infancy (≥ high school (HS) degree vs. < HS degree), was associated with lower lipid content ($\beta_{adjusted}$ = -1.44, 95% CI = -2.23, -0.66), higher water content ($\beta_{adjusted}$ = 1.06, 95% CI = 0.09, 2,03), and higher optical index ($\beta_{adjusted}$ = 0.62, 95% CI = 0.08, 1.17) in adult women with a BMI < 25 kg/m^2. These associations were adjusted for adulthood SES (education and income). No associations between early life SES and BTC were found in women with a BMI ≥ 25 kg/m^2 (**Table 2**).

Table 1. Associations of early life SES, as indicated by being in the highest vs. lowest category of SES index, and BTC in adolescent girls in the Columbia-BCERP Study

BTC Measure	**Overall** (n=165) $\beta_{adjusted}$ (95% CI)	**BMI < 25** kg/m^2 (n=95) $\beta_{adjusted}$ (95% CI)	**BMI ≥ 25** kg/m^2 (n=70) $\beta_{adjusted}$ (95% CI)	SES*BMI Interaction P-value
% Lipid	**-0.80 (-1.29, -0.32)**	**-1.14 (-1.97, -0.32)**	**-0.73 (-1.32, -0.14)**	0.85
% Water	0.18 (-0.32, 0.67)	0.67 (-0.02, 1.36)	-0.17 (-0.99, 0.65)	0.56
% Collagen	**0.58 (0.13, 1.03)**	0.60 (-0.12, 1.33)	0.57 (-0.03, 1.17)	0.37
Optical Index	0.40 (-0.80, 0.89)	0.58 (-0.15, 1.31)	0.52 (-0.19, 1.22)	0.86

Notes: Estimates are adjusted for race/ethnicity, age at BTC measurement, birthweight, household smoke exposure at birth, BMI-for-age z-score at age 7 years, and percent body fat at BTC measurement. Statistically significant estimates are bolded ($p<0.05$).

Table 2. Associations of early life SES, as indicated by maternal education in infancy (≥ HS vs. < HS degree), and BTC in women in the Columbia-BCERP Study

BTC Measure	**Overall** (n=158) $\beta_{adjusted}$ (95% CI)	**BMI < 25** kg/m^2 (n=31) $\beta_{adjusted}$ (95% CI)	**BMI ≥ 25** kg/m^2 (n=127) $\beta_{adjusted}$ (95% CI)	SES*BMI Interaction P-value
% Lipid	-0.21 (-0.52, 0.09)	**-1.44 (-2.23, -0.66)**	-0.05 (-0.38, 0.29)	**0.047**
% Water	**0.35 (0.01, 0.69)**	**1.06 (0.09, 2.03)**	0.18 (-0.20, 0.57)	0.11
% Collagen	0.03 (-0.33, 0.39)	0.17 (-0.13, 0.46)	0.01 (-0.44, 0.46)	0.94
Optical Index	0.12 (-0.21, 0.45)	**0.62 (0.08, 1.17)**	0.03 (-0.37, 0.44)	0.39

Notes: Estimates adjusted for race/ethnicity, age at BTC measurement, percent body fat at BTC measurement, and adulthood SES (education and income). Statistically significant estimates are bolded ($p<0.05$).

CONCLUSION: This study provides new evidence that early life SES is associated with BTC as early as adolescence. The direction of the associations is consistent with those for SES and breast cancer risk, suggesting that SES may influence breast cancer risk through mechanisms operating early in life, prior to reproduction.

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SUPPLEMENTAL BREAST CANCER SCREENING AFTER NEGATIVE MAMMOGRAPHY IN U.S. WOMEN WITH DENSE BREASTS

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INTRODUCTION:

Clinical consensus is lacking regarding how breast density should factor into supplemental testing after routine mammography screening (1). Supplemental screening has increased among U.S. women, likely due in part to greater awareness because of density notification laws (2). Ideally, women with the highest risk of breast cancer or poor outcomes after a diagnosis should receive supplemental screening.

OBJECTIVES:

Our purpose is to examine how supplemental screening use (ultrasound and/or MRI) after a negative mammogram among women with dense breasts varies by breast cancer risk factors and sociodemographic characteristics.

METHODS:

Analysis included exams (N=1,052,473) during 2011-2019 from registries in the Breast Cancer Surveillance Consortium (BCSC) where MRI (N=6) or ultrasound (N=3) was available for women aged 40-74 with a negative screening mammogram, dense breasts (BI-RADS c or d), and no personal history of breast cancer. We calculated the proportion of mammograms with supplemental screening within 12 months according to patient characteristics.

RESULTS:

Overall, 2.3% of negative mammograms in women with dense breasts had supplemental screening. Use was higher for younger women and among women with a prior breast biopsy (9.4% LCIS; 5.5% atypia; 3.3% without atypia; 2.2% unknown type vs 2.1% no prior biopsy). Use was nearly two times higher among women with a first-degree family history of breast cancer and those living in geographic areas (ZIP Codes) with greater median household income. MRI but not ultrasound use was higher among women with increasing 5-year breast cancer risk.

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Table 1: Use of supplemental screening after a negative mammogram among women with dense breasts, BCSC, 2011-2019

Characteristic	Use (%)
Overall	2.3%
Supplemental ultrasound/MRI	2.0/0.3%
Age (years)	
40-49/50-59/60-69/70-74	2.8/2.3/1.8/1.4%
Prior breast biopsy	
No vs Yes	2.1% vs 2.9%
Family history of breast cancer	
No vs Yes (first-degree)	2.0% vs 3.8%
Geocoded household income	
Quintile 1-3 (lower)/4/5 (higher)	1.7%/2.1%/3.3%
BCSC 5-year breast cancer risk	Ultrasound/MRI
<1.00% (low)	2.3/0.1%
1.00-2.49% (intermediate)	1.9/0.2%
2.50-3.99% (high)	1.9/0.6%
≥4.00% (very high)	2.3/1.4%

CONCLUSION:

The vast majority of US women with dense breasts do not obtain supplemental screening after a negative mammogram. Use was associated with area-level sociodemographic factors and breast cancer risk. Ongoing analyses are evaluating women's level of access to supplemental screening, use by facility characteristics, and examining trends in use over time relative to passage of density notification laws in each state where women reside.

What is the key new finding since 2019?

Among women with dense breasts, factors associated with breast cancer risk as well as socio-demographic factors such as income have an impact on whether women receive supplemental screening, which varies by modality. Supplemental screening with ultrasound was much more common than with MRI where both were available.

Does the new finding impact screening strategies for women?

This study underscores the need for evidence-based clinical practice guidelines concerning supplemental screening to better align use of breast imaging among patients most likely to receive benefit.

GLANDULAR TISSUE COMPONENT ON BREAST ULTRASOUND: A NEW IMAGING BIOMARKER FOR BREAST CANCER RISK

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INTRODUCTION:

Women with similarly dense breasts on mammography may have different subsequent risks of developing breast cancer due to varying degrees of lobular involution. A breast can be dense because it consists of predominantly duct and glandular components, which may contribute to a woman's risk; however, a breast may also be dense only due to tissue fibrosis, which will likely not affect the risk. Breast ultrasound (US) can assess the relative amount of glandular tissue component (GTC) to the fibrous stroma in dense breast parenchyma and can reflect the degree of lobular involution. The clinical practice of our institution and many other institutions in East Asia includes a description and classification of the GTC category in breast US reports, and GTCs are likely to be included in the next BI-RADS.

OBJECTIVES:

To describe the classification sonographic GTC and discuss the association between sonographic GTC and future risk of breast cancer in women with dense breasts.

METHODS:

Screening breast US examinations performed in women with no prior history of breast cancer and with dense breasts with negative findings from mammography from January 2012 to December 2015 were retrospectively identified. The GTC was reported as being minimal, mild, moderate, or marked at the time of the US examination. In women who had benign breast biopsy results, the degree of lobular involution in normal background tissue was categorized as not present, mild, moderate, or complete. The GTC-related breast cancer risk in women with a cancer diagnosis or follow-up after 6 months was estimated by using Cox proportional hazards regression. Cumulative logistic regression was used to evaluate the association between the GTC and lobular involution.

RESULTS: Among 8483 women (mean age, 49 years), 137 developed breast cancer over a median follow-up time of 5.3 years. Compared with a minimal or mild GTC, a moderate or marked GTC was associated with an increased cancer risk (hazard ratio, 1.5; 95% CI: 1.05, 2.1; P = .03) after adjusting for age and breast density. The GTC had an inverse association with lobular involution; women with no, mild, or moderate involution had greater odds (odds ratios of 4.9 [95% CI: 1.5, 16.6], 2.6 [95% CI: 0.95, 7.2], and 1.8 [95% CI: 0.7, 4.6], respectively) of a moderate or marked GTC than those with complete involution (P = .004).

CONCLUSION: The glandular tissue component was independently associated with the future breast cancer risk in women with dense breasts and reflects the lobular involution.

What is the key finding new since 2019? A higher GTC at screening breast US is associated with higher risk for breast cancer. A prospective multinational cohort study to validate the association of sonographic GTC and breast cancer risk has been published (ClinicalTrials.gov registration no. NCT05460975).

How does this finding impact screening strategies for women? Sonographic GTC information could identify the subset of women with dense breasts who are likely to benefit from supplementary screening.

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COMMUNICATING RISK VIA A BREAST CANCER SCREENING DECISION AID FOR WOMEN IN THEIR 40s WITH LIMITED HEALTH LITERACY

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INTRODUCTION:

Guidelines suggest that women in their 40s consider cancer risk and engage in shared decision making with their primary care provider (PCP) about when to initiate mammography screening.[1] While health literacy influences the ability to understand risk information and engage in shared decision making,[2,3] women with limited health literacy (LHL) are underrepresented in the development and testing of tools to support these activities.[4]

OBJECTIVES:

To develop an online interactive breast cancer screening decision aid (DA) that includes risk assessment and is appropriate for women with LHL.

METHODS:

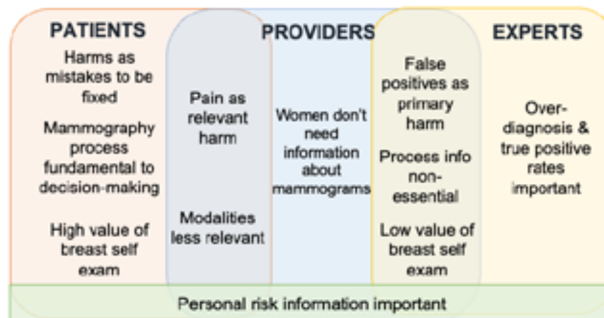
We engaged multiple national stakeholders and employed mixed methods to develop a breast cancer screening DA. Qualitative interviews with patients identified informational needs and preferences, while interviews with PCPs ascertained important features related to conducting SDM in clinical settings. A modified 3-round expert Delphi panel informed DA content and scope. Cognitive interviews conducted over two rounds with women with LHL refined and established acceptability of the DA.

RESULTS:

Interviews were conducted with 25 patients with LHL, 20 PCPs, and the Delphi panel consisted of 8 experts in breast cancer screening and decision science. Perceptions of mammography benefits, harms, and preferred DA content varied across stakeholders (Figure 1). Personal risk information was the only content desired by all 3 groups.

The DA, available at https://mymammogram.org, incorporates several patient-centered features and is written at a Grade 6.3 Flesh Kincaid grade level and a Gunning Fog index of 8.08. It includes risk assessment using the Gail Model, displays individual risk in relation to average risk, provides information about the process of receiving a mammogram, shares the risks and benefits of receiving a screening mammogram, and elicits and summarizes mammography preferences.

Figure 1: Desired DA Content by Stakeholder



CONCLUSION:

Engaging with patients, providers and experts, we created an acceptable patient-centered DA that incorporates personal risk information to assist women in their 40s in deciding when to begin mammography screening and how often to screen.

What is the key finding new since 2019?

Formative work highlights differences in patient, provider, and expert opinions and preferences for mammography DA content. The DA incorporates multiple stakeholder preferences to promote informed decision-making.

How does this finding impact screening strategies for women?

Our DA could be used to support women in their 40s in making risk- and preference-concordant breast cancer screening decisions.

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INTERIM RESULTS FROM SCREENTRUSTMRI - A RANDOMIZED CLINICAL TRIAL USING A COMBINATION OF AI MODELS AS A SELECTION TOOL FOR SUPPLEMENTAL MRI

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INTRODUCTION:

For the 8 to 10% of women who have 'extremely dense' breasts, undergoing magnetic resonance imaging (MRI) after negative mammography has been shown to reduce interval breast cancer by more than 80%.[1] A recent meta-analysis showed a median yield of 26 cancers per 1000 MRI exams.[2] With recent developments, applying artificial intelligence (AI) could provide an improved selection tool.

OBJECTIVES:

To examine the cancer yield of supplemental MRI using AI selecting a similar proportion of women as BIRADS 'extremely dense'. In this abstract we present interim results for women examined from April 1, 2021 to December 31, 2022.

METHODS:

Before the clinical trial started, three in-house AI models had been trained on a historic dataset of mammograms to classify risk, masking and visible cancer signs separately. The summary score, AISmartDensity, additionally included the Insight MMG model by Lunit Inc. The 92nd percentile (top 8%) of the score in the retrospective dataset defined the 'very high' category of AISmartDensity.

Figure 1. Workflow of the ScreenTrustMRI trial. After the particpant accepts the invitation, she is randomized to undergo MRI or not.

In the clinical trial, women with 'very high' AISmartDensity' and a negative screening mammography exam were invited to the study (Figure 1). After informed consent they were randomized to have MRI or not. The MRI exam was assessed by two radiologists. Women with BIRADS 3, 4 and 5 findings were recalled for second look ultrasound. If the lesion could not be identified on ultrasound, BIRADS 3 findings entered an MRI follow-up program while BIRADS 4-5 findings went for MRI-led biopsy.

Table 1: Findings in the first 536 breast MRIs

Assessment	Count	%	Cancer
BIRADS 1 or 2	449	83.8%	
BIRADS 3	50	9.3%	
BIRADS 4	23	4.3%	28
BIRADS 5	14	2.6%	

RESULTS:

Until December 31, 2022, we had invited 3610 women who had 'very high' AISmartDensity. 1316 (36%) accepted to participate. 658 were randomized to MRI, and 536 underwent MRI. Of these, 87 exams (16%) showed a BIRADS 3,4 or 5 finding, among which 28 cancers were diagnosed (Table 1). This corresponds to a positive predictive value of 32% and a cancer detection rate of 52 per 1000 MRI exams.

CONCLUSION:

AISmartDensity could increase the cancer yield for supplemental breast MRI after negative screening mammography.

What is the key finding new since 2019?

An AI pipeline selecting a similar proportion as BIRADS 'extremely dense' category, achieving a considerably higher cancer yield.

How does this finding impact screening strategies for women?

The decreased cost per cancer could make more providers offer breast MRI to screening participants who need it the most.

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ASSOCIATION OF BREAST CANCER WITH A FULLY-AUTOMATED MEASURE OF BACKGROUND PARENCHYMAL ENHANCEMENT

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INTRODUCTION:

A greater amount of fibroglandular tissue (FGT) in the breast is associated with increased breast cancer risk. On magnetic resonance imaging (MRI), the injection of a contrast agent causes portions of the FGT to enhance to varying degrees, an imaging feature known as background parenchymal enhancement (BPE). We and others have reported that the degree of BPE is associated with increased breast cancer risk.[1,2] However, the gold standard BI-RADS measure of BPE is subjective, reducing precision of estimates and potentially introducing bias into breast cancer risk assessment studies.

OBJECTIVES:

We aimed to evaluate the association between breast cancer and objectively-measured BPE, accounting for the amount of FGT and breast cancer risk factors.

METHODS:

The study population included women who received a bilateral breast MRI from 2010-2017 with no prior history of breast cancer. Breast cancer cases received a first breast cancer diagnosis at the time of or after their MRI; controls had no diagnosis of breast cancer for at least 6 months after the MRI. The unaffected breast of cases and a single breast of controls was used for analysis. Fully-automated software[3] was used to measure (A) FGT volume (cm^3) on the pre-contrast series; and (B) "BPE extent," defined as the proportion of FGT enhancing >20% on the first post-contrast series. We assessed the correlation between radiologist-assessed BI-RADS BPE and quantitative BPE extent. The association between breast cancer and BPE extent was estimated in multivariable models, adjusting for FGT volume, fat volume, and breast cancer risk factors.

RESULTS:

There were 536 cases and 939 controls. Our quantitative measures of BPE extent and FGT volume were uncorrelated. BPE extent was correlated with BI-RADS BPE ($r = 0.54$, $p<0.001$). In the multivariable model (**Table 1**), BPE extent was statistically significantly associated with breast cancer (OR=1.7, 95% CI 1.2-2.5). There were no differences in the association within subgroups defined by menopausal status (interaction P-value=0.73) or FGT volume (P =0.64).

Table 1. Multivariable-adjusted associations of breast cancer with BPE extent and FGT volume

Characteristic	OR[a]	95% CI
BPE extent, (range, %)		
Tertile 1[c] (2.9 to 34.2)	—	—
Tertile 2 (34.3 to 50.6)	1.4	1.0, 2.0
Tertile 3 (50.7 to 97.3)	1.7	1.2, 2.5
FGT volume (range, cm^3)		
Tertile 1 (0.7 to 60.4)	—	—
Tertile 2 (60.5 to 145.8)	1.5	1.1, 2.1
Tertile 3 (145.9 to 2,062.2)	1.4	1.0, 2.0

[a] Odds ratio (OR) for breast cancer estimated in logistic regression model including measures in table with adjustment for fat volume (cm^3), age at MRI, recruitment site, race/ethnicity, menopausal status; parity; history of lobular carcinoma in situ (LCIS) or benign breast disease; mutations in *BRCA1*/*BRCA2*; MRI view (axial vs. sagittal); and year.

CONCLUSION:

Our reproducible, quantitative BPE measure predicts breast cancer as well as or better than the BI-RADS gold standard.[1] BPE is a promising marker to refine breast cancer risk assessment beyond FGT alone.

What is the key finding new since 2019?

Prior studies reported a possible association between breast cancer and BPE assessed on the BI-RADS scale. We showed that an objective BPE measure is associated with breast cancer independently of FGT.

How does this finding impact screening strategies for women?

This objective BPE measure, used jointly with the amount of FGT, could be used to improve breast cancer risk assessment and ultimately enable personalization of breast cancer screening programs.

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REPRODUCIBILITY OF VOLUMETRIC FIBROGLANDULAR FRACTION IN DEDICATED CONE-BEAM BREAST CT

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INTRODUCTION:

Dedicated cone-beam breast CT (BCT) is an emerging imaging modality that provides fully 3D images of the uncompressed breast. It has been shown to improve sensitivity over mammography for diagnostic workup and is US FDA-approved for diagnostic imaging. In an effort to translate BCT for screening, advanced image reconstruction techniques are being pursued. Radiographic breast density is an established risk factor for breast cancer, and the fully 3D images from BCT make it readily amenable to quantify the breast density in an objective manner.

OBJECTIVES:

To investigate the reproducibility of volumetric fibroglandular fraction (VGF),[1] defined as the proportion of fibroglandular tissue volume relative to the total breast volume excluding the skin, across four image reconstruction techniques.

METHODS:

Projection datasets from 106 women who participated in a prior clinical trial (NCT01090687) and acquired using a pre-FDA approval prototype (KBCT1000) were reconstructed to a fixed isotropic voxel size of $(0.273\ \text{mm})^3$ using four algorithms: the analytical FDK method, which is the standard method used for clinical interpretation; a compressed sensing-based fast, regularized, iterative statistical technique (FRIST); a fully-supervised multi-scale residual dense network (MS-RDN) deep-learning algorithm; and, a self-supervised deep-learning algorithm (Noise2Noise, N2N). From each reconstructed breast volume, the skin was first segmented and removed, followed by segmentation and classification of adipose and fibroglandular tissues using a kernel-based fuzzy c-means algorithm, to calculate the VGF.[1] The distribution of BI-RADS density categories 1–4 assessed from mammography were 7%, 38%, 34%, and 22%, respectively.

RESULTS:

Summary statistics of the VGF are in Table 1. For the repeated measures of matched datasets, VGF did not differ among the four reconstructions (P=0.167, Friedman's test). None of the three advanced reconstruction algorithms differed from the standard FDK reconstruction in terms of VGF (P>0.862).

Table 1: VGF from four image reconstructions (n=106; IQR – Inter-quartile range; p-values from Dunn's multiple comparisons test)

Reconstruction Method	Median (IQR) [Range]	p-value
FDK	0.186 (0.122, 0.239) [0.04 – 0.505]	NA
FRIST	0.18 (0.131, 0.235) [0.07, 0.417]	0.936
MS-RDN	0.187 (0.129, 0.235) [0.043 – 0.409]	0.862
N2N	0.193 (0.133, 0.235) [0.047 – 0.487]	>0.999

CONCLUSION:

The VGF from advanced reconstruction algorithms does not differ from the FDK reconstruction used in current clinical practice.

What is the key finding new since 2019?

Advanced reconstruction algorithms being developed for low-dose cone-beam breast CT-based screening reproduces the VGF for quantitative breast density-based risk estimation.

How does this finding impact screening strategies for women?

When breast CT is translated for screening, quantitative breast density (VGF) can be obtained to enable risk-based screening.

ACKNOWLEDGMENTS:

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Harmonization of site effects in image-derived features for multicenter mammography studies

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INTRODUCTION:

Radiomics, the high-throughput extraction of quantitative features from medical images, is a promising approach for characterizing breast parenchymal complexity to improve breast cancer risk assessment [1]. While multicenter studies are needed, such datasets often contain technical variability in image acquisition and processing across sites, referred to site effects [2]. ComBat is a statistical method for correcting or "harmonizing" site effects in image-derived features while "protecting" linear effects of clinical covariates [2].

OBJECTIVES:

We assess the utility of ComBat in adjusting for site effects from radiomic features extracted from a multicenter mammography study.

METHODS:

We randomly selected 100 patients from each of the 14 combinations of center and study year from a larger dataset of full-field digital mammography (FFDM) exams collected at the Hospital of the University of Pennsylvania/UPENN (2011-12) and the Mayo Clinic, Rochester (2006-17). A validated software pipeline was used to automatically extract 1026 features. ComBat was applied to adjust for "site effects" due to differences in center and study year, where the covariates age, average fibroglandular volume, and body mass index were protected [2].

Table 1: Percentage of features with significant ($p<0.05$) differences in distribution due to site/study year detected using the Anderson-Darling test before and after ComBat.

	Site/Study Year
Original	95.8%
ComBat	13.6%

Harmonization performance was evaluated using the Anderson-Darling test (alpha = 0.05) for differences in distribution due to site effects for each feature. The Robust Effect Size Index (RESI) for a linear model was used to quantify the effect size for site effects before and after harmonization [3].

RESULTS:

ComBat harmonization reduced the percentage of features with significant differences in distribution due to site effects (**Table 1**). Harmonization also reduced the magnitude of the effect size for the site variable, a trend represented by **Figure 1** for acquisition at UPENN in 2011.

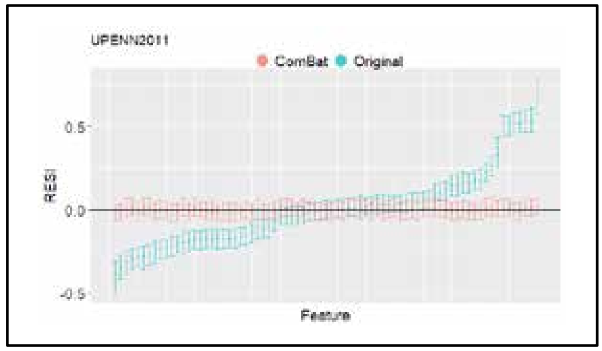

Figure 1. Effect size for sample acquisition at UPENN in 2011 before and after ComBat harmonization for 75 randomly selected features. RESI values closer to 0 indicate reduced effect of site on feature and greater feature robustness to site.

CONCLUSION:

In this work, we demonstrate that standard ComBat can be used for better standardization of radiomic features in multicenter mammography studies to improve reproducibility by reducing distributional differences and effect sizes due to site effects.

What is the key finding new since 2019?

ComBat is an effective method for removing batch effects due to site differences in radiomic features extracted from multicenter mammography studies.

How does this finding impact screening strategies for women?

Using ComBat to adjust for differences in site will result in greater model generalizability, enabling greater clinical translation of radiomics tools to improve breast cancer risk assessment.

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ASSOCIATIONS OF STEM CELL MARKERS CD44, CD24, AND ALDH1A1 IN BENIGN BREAST BIOPSIES WITH MAMMOGRAPHIC BREAST DENSITY

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INTRODUCTION:

Mammographic breast density is a well-established, strong breast cancer risk factor but the biology underlying this association remains unclear. A stem cell hypothesis of breast carcinogenesis suggests that breast cancer development might be directly related to the size of the stem cell pool and its mitotic activity. Whether mammographic breast density may reflect underlying alterations in the size and activity of the breast stem cell pool in the breast is unknown.

OBJECTIVES:

We examined associations of CD44, CD24, and aldehyde dehydrogenase family 1 member A1 (ALDH1A1) breast stem cell markers with mammographic breast density.

METHODS:

This study included 218 cancer-free women with biopsy-confirmed benign breast disease within the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts. The data on breast cancer risk factors were obtained from biennial questionnaires. Immunohistochemistry (IHC) was done on tissue microarrays. For each core, the IHC expression was assessed using a semi-automated platform, Definiens Tissue Studio, and expressed as % of cells that stain positively for a specific marker out of the total cell count. Positivity was assessed separately for epithelium and stroma in cores from the areas of normal terminal duct-lobular units (TDLUs). Mammographic breast density was assessed with computer-assisted techniques. Generalized linear regression was used to examine the associations of each stem cell marker (continuous and categorical as $\geq$10 vs. <10%) with square root-transformed percent density, absolute dense and non-dense areas, adjusted for breast cancer risk factors.

RESULTS:

Staining results for stroma were available for 195, 201, and 192 women for CD44, CD24, and ALDH1A1, respectively; the staining results for epithelium were available for 180, 189, and 183 women, respectively. In multivariate analysis, CD44 and ALDH1A1 expression in stroma was positively associated with percent breast density ($\geq$10 vs. <10% β=0.54, 95% Confidence Interval [CI] 0.03; 1.06 and β=0.73, 95% CI 0.20; 1.27, respectively) and was inversely associated with non-dense area (β per 10% increase= -0.17, 95% CI -0.34; -0.01 and β for $\geq$10% vs. <10%= -1.13, 95% CI -2.02; -0.25, respectively). CD24 expression in stroma and epithelium was positively associated with non-dense area (β per 10% increase=0.36, 95% CI 0.01; 0.70 and β=0.34, 95% CI 0.11; 0.57, respectively). The findings remained similar when the models were additionally adjusted for the time between biopsy and mammogram dates. No associations were observed with absolute dense area.

CONCLUSION:

Mammographic breast density may be reflective of stem cell activity in the breast.

What is the key finding new since 2019?

CD44, CD24, and ALDH1A1 expression in benign breast biopsies is associated with mammographic breast density.

How does this finding impact screening strategies for women?

As stem cell activity is potentially modifiable via a variety of targeted therapies, if confirmed, these findings could translate into stem cells-directed pharmaceutical interventions aimed at reducing breast density, and thus, improving mammographic sensitivity in women with dense breasts.

POLYGENIC SCORE PREDICTS EARLY ONSET TRIPLE-NEGATIVE BREAST CANCER IN BLACK WOMEN

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INTRODUCTION:
Black women in the U.S. often develop earlier, more biologically aggressive breast cancers (BC). Triple negative breast cancer (TNBC) is an especially aggressive form of BC which is twice as common in Black women than white women and often occurs earlier, before screening would be recommended. Improved risk prediction methods are urgently needed for more effective identification of young Black women with elevated risk of TNBC.

OBJECTIVES:
We previously described development and clinical validation of a multiple-ancestry PRS (MA-PRS) that is based on individual genetic ancestral composition. MA-PRS has been integrated into the Tyrer-Cuzick model for use in clinical practice and has been shown to substantially improve BC risk prediction. Here, we evaluated the extent to which MA-PRS can improve upon clinical factors for prediction of TNBC, and early onset (<50 years) TNBC, in a large cohort of self-reported Black women.

METHODS:
We examined clinical and genetic records from self-reported Black women who were referred for hereditary cancer testing from June 2020 through December 2022 and negative for pathogenic variants in genes associated with BC. MA-PRS was calculated as previously described based on 149 SNPs (93 BC and 56 ancestry-informative). The association of MA-PRS with TNBC was analyzed using logistic regression adjusted for personal and family cancer history, age, and genetic ancestry. Women with invasive BC who did not indicate TNBC status were excluded from analysis. Analyses were conducted within the full cohort and within the subpopulation of patients < 50 years old. Odds ratios (ORs) are reported per standard deviation (SD). P-values are based on likelihood ratio chi-square statistics and reported as two-sided.

RESULTS:
We identified 20,585 women who met study eligibility criteria. Nearly one-third (6,318/20,585) of patients had a first-degree relative affected by BC. More than 60% (13,987/20,585) of patients were under the age of 50. There were 1,226 (6.0%) patients diagnosed with TNBC in the full cohort, and 427 (3.1%) among women less than 50 years old.

MA-PRS significantly improved TNBC risk prediction over clinical factors in the full cohort, and in the subpopulation of women under 50 years old (Table 1). Women in the top 5% of the MA-PRS distribution were at nearly 2-fold increased risk of TNBC (Table 1).

CONCLUSION:
Clinical implementation of risk prediction models that incorporate MA-PRS may lead to more effective identification of women at risk of TNBC.

Table 1: Association of MA-PRS with TNBC after accounting for clinical factors

Cohort (N)	OR per SD (95% CI)	p-value	Average OR per SD in top 5%
All patients (20, 585)	1.29 (1.20, 1.38)	1.8×10^{-13}	1.68
< 50 years old (13,987)	1.38 (1.23, 1.54)	1.3×10^{-8}	1.93

What is the key finding new since 2019?
MA-PRS may aid in early identification of young Black women at risk for TNBC.

How does this finding impact screening strategies for women?
Risk assessment is critical for identifying young Black women who may benefit from germline genetic testing and enhanced surveillance. Incorporation of the MA-PRS into traditionally used risk assessment models can improve the identification of women at the highest risk of developing aggressive breast cancers such as TNBC.

Breast Cancer Risk Assessment Improves by Combining Artificial Intelligence for Lesion Detection and Mammographic Texture-based Risk

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INTRODUCTION:

Personalized breast cancer screening tailored to the individual woman's risk of breast cancer might improve screening quality and facilitate better exploitation of radiologists' resources[1]. Safe clinical implementation of personalized screening requires reliable risk models with readily available co-variates. Recent mammography-based deep learning (DL) models can estimate short- or long-term risk[2].

OBJECTIVES:

This study investigated whether risk assessment improved when combining a diagnostic artificial intelligence (AI) system and mammographic texture risk model. The AI system, developed for abnormal lesion detection, was used to detect subtle localized signs of developing cancer to estimate short-term risk. The texture model, developed to measure systemic differences in breast tissue between high- and low-risk women, estimated long-term risk.

METHODS:

This study examined a Danish screening sample of consecutively screened women, with negative screening examination, in a study period from Nov. 2012 to Dec. 2015 with at least five years of follow up. The diagnostic AI system Transpara® (v1.7.0, ScreenPoint Medical) generated exam scores indicating likelihood of cancer, intended as a surrogate for short-term risk. A mammographic texture model trained on independent data, assessed long-term risk[3]. Exam scores and texture risks were evaluated individually and aggregated using a neural network to determine a joint short- and long-term risk in mammograms from the study period. Risk assessments were evaluated for interval cancers (IC) within two years from screening and long-term cancers (LTC) diagnosed two years after screening until end of follow-up.

RESULTS:

From a Danish screening sample (n=118,751), 320 women developed IC and 1,401 developed LTC. The combination model achieved a higher AUC for ICs than the exam score (0.78 vs. 0.75, P<0.001) and texture risk (0.78 vs. 0.71, P<0.001).

Table 1: AUC for the different risk models.

Model	AUC(IC)	AUC(LTC)
Exam score (1)	0.75 (0.72, 0.78)	0.69 (0.68, 0.71)
Texture risk (2)	0.71 (0.68, 0.74)	0.65 (0.64, 0.67)
(1) + (2)	0.78 (0.75, 0.80)	0.71 (0.70, 0.73)
(1) + (2) + age + PMD	0.77 (0.75, 0.80)	0.72 (0.71, 0.73)

The combination model achieved a higher AUC for LTCs than the exam score (0.71 vs. 0.69, P<0.001) and texture risk (0.71 vs. 0.65, P<0.001). Adding age and percentage mammographic density (PMD) to the combination model yielded a higher AUC for LTCs (0.71 vs. 0.72, P=0.03). 10% of women with highest combined risk accounted for 44.7% of ICs and 33.7% of LTCs.

CONCLUSION:

Combining a diagnostic AI system and mammographic texture model improved risk assessment for ICs and LTCs.

What is the key finding new since 2019?

Combing mammography-based DL risk models improved risk assessment and the combination model generalized across screening populations and mammographic devices[3].

How does this finding impact screening strategies for women?

Using screening mammograms only, the combination model could support risk-stratified screening to identify, e.g., high risk women.

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EFFECTIVENESS OF BREAST DENSITY EDUCATIONAL INTERVENTIONS ON MAMMOGRAPHY SCREENING ADHERENCE AMONG LATINAS: A RANDOMIZED CONTROLLED TRIAL

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INTRODUCTION

Mammographic breast density (MBD) is the strongest independent predictor of breast cancer (BC), including in Latina populations.[1-2] Latinas are less likely to be adherent to mammography screening.[3] Interpersonal cancer education interventions delivered by a *Promotora* are increasingly used to promote adherence to mammography screening among Latinas.[4]

OBJECTIVES:

The purpose of this randomized control trial (RCT) was to compare adherence to attending the next routine screening mammogram between three different breast density notification approaches. We hypothesized that Latinas randomized to receive a MBD notification letter accompanied by written education materials and an interaction with a Promotora would be more likely to be adherent.

METHODS:

This RCT was conducted at one of the largest federally qualified health centers (FQHC) in Phoenix, Arizona. Eligible women were randomized 1:1:1 to usual care (UC; a standard mailed notification letter), enhanced care (ENH; notification letter + educational brochure), or interpersonal care (INT; standard clinical notification letter + educational brochure + telephone-based Promotora education). Surveys analyzed were administered at enrollment (T0) and 1 year post randomization (T2). This analysis was limited to Latinas enrolled and randomized between October 27, 2016 to December 21, 2018 (n=946; 66.1% <50 years of age, 53.5% with MBD).

RESULTS:

Adherence rates at 1- (UC 23.4%, ENT 25.1%, INT 28.3%) and 2-year (UC 51.4%, ENT 52.7%, INT 54.9%) post-baseline were similar across the study groups. Latinas randomized to the INT or ENT were not more likely to be adherent to subsequent mammography compared to Latinas randomized to UC (ENT HR: 1.03 [95% CI 0.8, 1.3], INT HR: 1.10 [95% CI - 0.9, 1.4], p=.7)

CONCLUSION:

Interventions targeting breast density education alone are unlikely to result in significant improvement in mammography adherence among Latinas receiving care in FQHCs.

What is the key finding new since 2019?

This study is one of the first to evaluate the effectiveness of a three-arm educational intervention to improve mammography adherence among Latina women receiving care in a FQHC.

How does this finding impact screening strategies for women?

Education along with strategies such as patient reminders, personalized BC risk assessments, and provider recommendations are likely needed to improve BC screening adherence among underserved Latinas.

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Risk perceptions and mammography screening behavior among underserved, Hispanic women: Implications for risk-based screening.

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INTRODUCTION:

Risk-based screening has the potential to increase mammography use and reduce breast cancer (BC) disparities among underserved, Hispanic women.[1] Perceived risk may play a key role in mammography screening behavior, but evidence among Hispanic women remains mixed. Given calls for risk-based screening, there is need to disentangle the relationship between perceived risk and mammography screening behavior.

OBJECTIVES:

To assess the association between three measures of perceived risk (comparative risk, ordinal lifetime risk, and percent lifetime risk) with mammography screening behavior. We hypothesize that lower levels of perceived risk will be associated with reduced frequency of mammography screening.

METHODS:

This is a secondary, cross-sectional analysis of self-reported baseline survey data from an NIH-funded randomized trial conducted at a large Federally Qualified Health Center in Arizona. [2] Between October 2016 and October 2019, 1329 women with no prior history of BC completed a baseline survey including three validated item measuring perceived risk and two items assessing mammography screening behavior (e.g., ever had a mammogram, # prior mammograms). Ordinal logistic regression models stratified by age (<50 and 50+) were used to examine associations between mammogram screening behavior (0-1, 2-4, 5+: dependent variable) and the three measures of perceived risk (independent variables), adjusting for age, family history, language, and breast biopsy history. Odds ratios and 95% confidence intervals are reported based on the odds of having more vs fewer mammograms.

RESULTS:

Overall, 75% reporting their percent lifetime risk between 0-10%, 96% reporting their ordinal risk not high, and 50% reporting their comparative risk as much lower. We found no association between the perceived risk and mammography screening behavior for women <50. In women 50+, percent lifetime risk (>10% vs 0-10%) was significantly associated with more prior mammograms (adjusted OR 1.6, CI 1.0, 2.5, p=.05), but comparative risk and ordinal lifetime risk were not. Data also show minimal alignment between women's self-reported comparative risk vs. ordinal lifetime risk vs. percent lifetime risk.

CONCLUSION:

Underserved, Hispanic, and primarily Spanish-speaking women's perception of BC risk was low and did not have a strong association with mammography screening behavior.

What is the key finding new since 2019?

Risk perceptions may play less of a role on mammography screening behavior compared to other factors. Findings also suggest the need for better measures of risk perception, particularly among primarily Spanish-speaking, Hispanic women.

How does this finding impact screening strategies for women?

Strategies targeting women's understanding of BC risk, in addition to strategies targeting other barriers to screening, are essential for implementing risk-based screening approaches for BC.

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ARTIFICIAL INTELLIGENCE FOR IMAGE-BASED BREAST CANCER RISK PREDICTION USING ATTENTION

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INTRODUCTION:

Breast screening can detect cancers before they become symptomatic, but we expect improved performance by personalization according to individual risk. We focus on mammographic appearance assessed by deep learning.

OBJECTIVES:

Develop a short-term breast cancer risk model utilizing transfer learning from screen-detected cancers that

- is not reliant on expert annotations of training images
- incorporate high resolution image information

We proposing a transfer-learning enabled Multiple Instance Learning (MIL) model with attention-based aggregation. MIL reduces the computational burden by converting images to a bag of instances. The attention module does not require expert annotations, but it can highlight areas of interest which provides explainability.

METHODS:

We train on 1452 images (1082 normal, 370 screen detected cancer) from the Predicting Risk of Cancer at Screening study [1]. Each image is split into 224x224 pixel overlapping patches that are then fed into a CNN-based feature extractor. The resulting feature vectors are aggregated using one of two methods shown in Figure 1. We test on a priors set which consists of women confirmed cancer free at the time who then go on to develop breast cancer in the next 5 to 55 months. There are 1280 such images with 320 positives. Both sets are case-control matched on age, BMI, parity and menopausal status to ensure an even distribution of variables associated with risk.

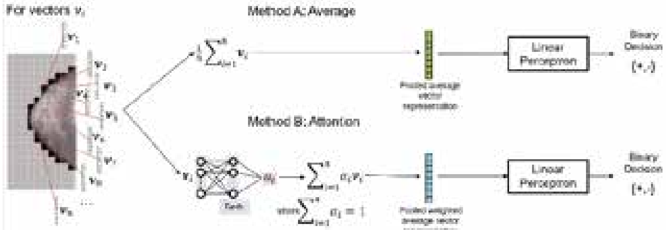

Figure 1. Instance aggregation

***Joint last author**

RESULTS:

Table 1 shows the AUC and 95% confidence intervals for the two methods. Figure 2 displays qualitative results as saliency maps produced by the attention module.

Table 1. Results

	View	AUC(SDC)	AUC(prior)
Average	CC	0.534 (0.499,0.569)	0.526 (0.489,0.564)
	MLO	0.502 (0.466,0.534)	0.496 (0.458,0.533)
	Combined	0.527 (0.492,0.561)	0.511 (0.473,0.548)
Attention	CC	0.769 (0.740,0.797)	0.627 (0.592,0.663)
	MLO	0.778 (0.748,0.808)	0.617 (0.583,0.651)
	Combined	**0.804** (0.777,0.830)	**0.635** (0.600,0.669)

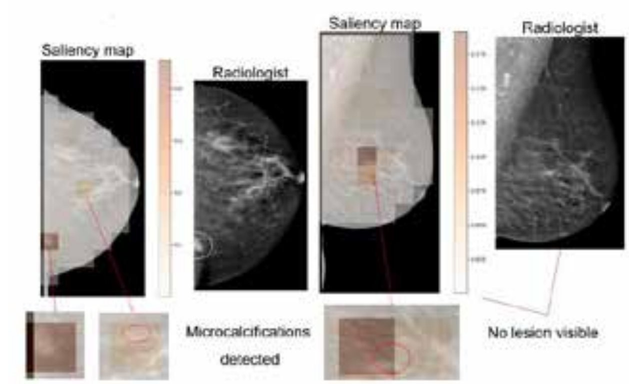

Figure 2. Saliency maps produced by our model compared with annotations by an independent radiologist.

CONCLUSION:

Mammograms showing screen-detected cancers are a viable substitute for the prior mammograms when developing deep learning risk models. Additionally, attention-based aggregation can learn to detect cancer signs without expert annotations.

What is the key finding new since 2019?

A model trained to detect cancers in mammograms can be utilized to predict risk from short-term priors.

How does this finding impact screening strategies for women?

Accurate prediction of individual breast cancer risk can pave the way for more personalized screening.

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Predicting breast cancer with MRI for individual risk-adjusted screening and early detection

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INTRODUCTION:

Women with an increased life-time risk of breast cancer undergo supplemental annual screening MRI in the United States. We propose a new framework to determine an individual's probability of developing breast cancer within a defined period of time based on the current MRI to reduce the burden of screening and to allow early detection of cancer.

OBJECTIVES:

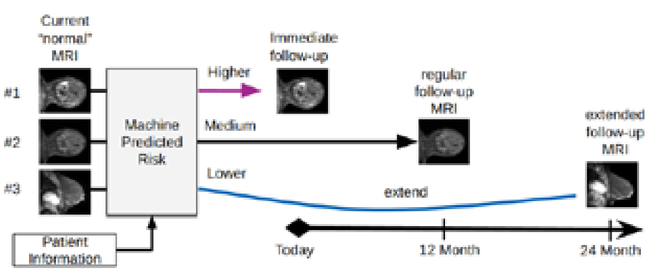

Figure 1. The risk of a future lesion is predicted based on the current MRI exam and patient information

We propose a framework for individualized breast cancer screening using yearly breast MRI exams. The framework recommends either extending the interval of the next exam or immediate follow-up to detect malignant lesions earlier. We argue that reducing screening burden and early detection are not in opposition, and the follow-up period should be adjusted based on individual patient's risk. The results of the study extend to any adaptive screening schedule. Proof-of-principle results were obtained using a retrospective set of screening breast MRI exams from a large patient sample.

METHODS:

We trained a risk-prediction network using exams from 12,694 women including screening and diagnostic exams. To account for the low amount of screen-detected cancers (~1%) we first pre-trained a segmentation network to isolate regions of concern in a volume. Then trained a diagnostic exams to classify these regions. Finally, we fine-tuned this network using a screening population with one-year follow-up containing 163 screen-detected cancers in a total of 9 350 exams. The resulting risk predictions were grouped into low/medium/high risk based on cut-off values of negative and positive predictive value.

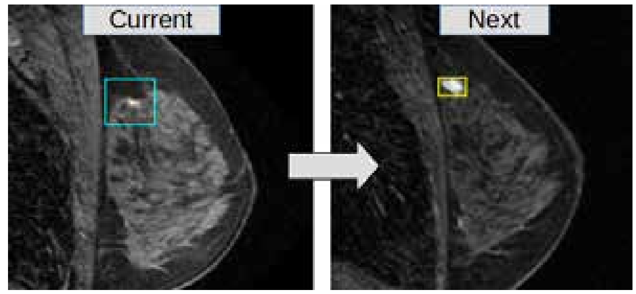

Figure 2. The network predicts the location of a region of concern (blue box) in a benign exam, which developed cancer in the next scheduled exam (yellow box).

RESULTS:

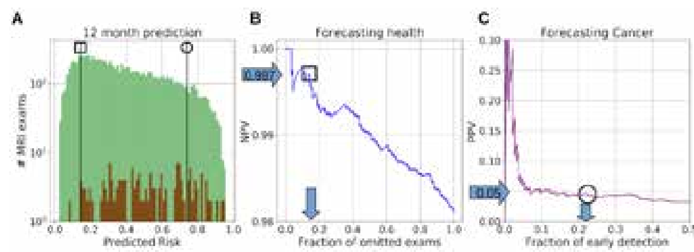

Figure 3. A. Predictions of the network in a benign population with 1-year follow-ups including 167 patients that developed cancer. B. At a negative predictive value of 95% we can extend the screening interval of 16% of exams while maintaining the screen-detected cancer rate. C. At a positive predictive value of 5%, we can potentially detect 33% of developing cancers one exam early.

CONCLUSION:

The study used a screening dataset of 9,183 exams to test a machine's ability to identify regions of concern that coincided with future tumors. The machine detected 79% of screen-detected cancers in the previous exam, and reevaluating regions of concern in 10% of cases could have resulted in 56 early detections by a radiologist. Screening burden could have been reduced in 16% of cases without compromising the interval cancer rate.

How does this finding impact screening strategies for women?

This approach has the potential to improve screening strategies for women by proposing a patient specific risk-adjusted screening, that can reduce the screening burden and simultaneously increase early detection of breast cancer.

ULTRASOUND TOMOGRAPHY MEASURES OF BREAST DENSITY DECLINE BY TREATMENT-ASSOCIATED ENDOCRINE SYMPTOMS AFTER TAMOXIFEN THERAPY: EXPLORING THE ROLE OF *CYP2D6* PHENOTYPE AND TAMOXIFEN METABOLITES

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INTRODUCTION:

Breast density decline with tamoxifen therapy is associated with greater therapeutic benefit.[1] Recent data suggest that women with tamoxifen-associated endocrine symptoms may experience greater reductions in breast density.[2] *CYP2D6*, an enzyme that metabolizes tamoxifen to 4-hydroxy-tamoxifen and endoxifen, may play an important role.

OBJECTIVES:

We aimed to evaluate changes in breast density by treatment-associated endocrine symptoms among women prescribed tamoxifen in a 12-month longitudinal study. We examined the distribution of tamoxifen metabolites at 12-months by *CYP2D6* phenotypes; we further examined whether results persisted for efficient or intermediate metabolizers.

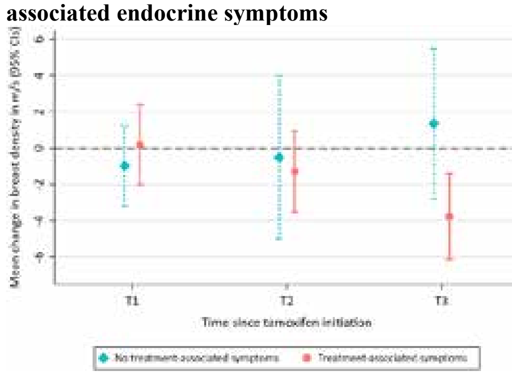
METHODS:

Treatment-associated endocrine symptoms and sound speed measures of breast density, assessed via novel whole breast ultrasound tomography (m/s),[3,4] were ascertained before tamoxifen (T0) and at 1-3 (T1), 4-6 (T2), and 12 months (T3) after initiation among 60 women, aged 30-70 years, enrolled in the Ultrasound Study of Tamoxifen at the Karmanos Cancer Institute and Henry Ford Health Systems (Detroit, MI). DNA was extracted from saliva samples and *CYP2D6* was sequenced on the PacBio SMRT platform to facilitate direct haplotyping of the entire gene-locus, producing reliable diplotypes. Corresponding *CYP2D6* phenotypes were categorized as poor, intermediate, or efficient metabolizers. Serum (Z)-tamoxifen, (Z)-N-desmethyl-tamoxifen, (Z)-4OH-tamoxifen, and (Z)-endoxifen were measured at T3 using liquid chromatography-tandem mass spectrometry; median (range) are reported for tamoxifen metabolites by *CYP2D6* phenotype. We estimated multivariable-adjusted mean change in breast density by treatment-associated endocrine symptoms, overall and among efficient/intermediate metabolizers.

RESULTS:

Significant breast density declines were observed in women with treatment-associated endocrine symptoms (p-trend=0.007), but not among women without symptoms (p-trend=0.20) (p-interaction=0.02) (**Figure**).

Figure: Mean change in breast sound speed (m/s) by treatment-associated endocrine symptoms



Efficient *CYP2D6* metabolizers had higher levels of endoxifen, the most potent metabolite, compared with poor or intermediate metabolizers (Table). Density declines persisted among efficient/intermediate metabolizers.

Table: Distribution of tamoxifen metabolites by *CYP2D6* phenotypes

Median (range)	Poor	Intermediate	Efficient
(Z)-4OH-tamoxifen (ng/ml)	1.64 (0.88, 2.36)	1.34 (0.25, 2.77)	1.41 (0.25, 6.78)
(Z)-endoxifen (ng/ml)	3.02 (2.29, 4.16)	6.03 (0.62, 24.60)	9.59 (0.25, 32.4)
(Z)-N-desmethyl tamoxifen (ng/ml)	256.5 (200.0, 487.0)	212.0 (68.6, 652.0)	230.0 (2.50, 280.0)
(Z)-tamoxifen (ng/ml)	147.0 (89.9, 266.0)	126.0 (15.8, 320.0)	115.0 (2.50, 337.0)

Note: Analytic sample had two women with indeterminate *CYP2D6* status and no ultra metabolizers

CONCLUSION:

These findings may provide mechanistic insights into endocrine symptoms and breast density declines after tamoxifen therapy. Further studies are needed to assess whether endocrine symptoms may be a proxy for tamoxifen response across all *CYP2D6* phenotypes.

What is the key finding since 2019?

Women with tamoxifen-associated endocrine symptoms experienced greater declines in breast density than those without symptoms, and declines remained among efficient and intermediate *CYP2D6* metabolizers.

What are the clinical implications?

Further studies are needed to assess whether these findings predict clinical outcomes. If confirmed, endocrine symptoms may be a proxy for tamoxifen response and useful for patients and providers to encourage adherence.

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Alcohol consumption during adolescence modifies the composition of the breast.

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INTRODUCTION:

Alcohol consumption is a strong risk factor for pre and post-menopausal breast cancer (BC) and drinking before first birth is associated with BC independent of drinking habits after this period[1].
Also, alcohol intake during adulthood is positively associated with breast composition, it increases the % of fibroglandular volume (%FGV) and the absolute fibroglandular volume (AFGV) in pre and postmenopausal women[2]. These associations, between alcohol and breast density, remain even after adjusting by body mass index (BMI)[3]. However, data in relation to alcohol consumption during adolescence is inconclusive, mainly because data is collected retrospectively and it could be affected by recall bias[4].

OBJECTIVES:

We have prospectively measured alcohol consumption and breast composition in 400 Chilean adolescent females. Thus, our aims are to:
1) describe alcohol consumption (a. ever alcohol consumption, b. Age at first alcohol consumption, c. Time of the last consumption, d. How many times the participant drank alcohol in the last 30, and e) Quantity of alcohol consumed in the last month) during adolescence (16y) and
2) to assess the association between alcohol consumption with %FGV and AFGV during adolescence.

METHODS:

We performed a cross-sectional study within the Growth Obesity Chilean Cohort Study, which is an ongoing cohort of low-income adolescents born in 2002-2003 in the South-East Area of Santiago. They have been extensively evaluated since they were 4y of age to understand early origins of diet-related chronic diseases. In 2016-2018, we collected data on anthropometry (weight and height), applied the National Survey of Drugs developed by the National Service for the Prevention and Rehabilitation of Drug and Alcohol Consumption (SENDA) to measure alcohol intake. Breast composition was measured by dual X-ray absorptiometry (DXA) (n=303).
Liner regression models were performed to estimate ß coefficients and 95%CI. Models were adjusted by nutritional status, birth weight, and maternal education.

RESULTS:

Adolescents who reported alcohol consumption (YES/NO) had higher %FGV compared to those who never consumed (β 3.9; 95% CI: 1.2; 6.7). Adolescents who started consumption before the age of 13 years had higher %FGV compared to those who never consumed (β: 5.0, 95% CI: 1.1; 8.8). No statistically significant associations were found with AFGV.

CONCLUSION:

Although the pattern of association between alcohol consumption and breast density at young ages is still not clear, our study shows a relationship between early alcohol consumption in adolescents and changes in breast composition. Promoting effective actions to avoid alcohol drinking at young ages may impact breast cancer incidence.

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FEASIBILITY OF QUANTITATIVE BREAST DENSITY MEASUREMENTS IN OBESE WOMEN WITH DEDICATED CONE-BEAM BREAST CT

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INTRODUCTION:

Breast density is an established risk factor for breast cancer and has been used as a surrogate endpoint biomarker to evaluate breast cancer preventive strategies. Accurate breast density measurement by mammography is limited by overlapping breast tissue from breast compression. This is especially relevant to obese women because obesity is positively correlated with increased compressed breast thickness on mammograms. In a previous study of metformin in overweight/obese women with components of metabolic syndrome, breast density was assessed by fat/water MRI as it provided 3D images of the breast without compression[1]. However, density measures could not be obtained from a notable proportion of study participants. Dedicated cone-beam breast CT (BCT) is an emerging imaging modality that provides fully 3D images of the uncompressed breast enabling quantification of fibroglandular tissue volume (FV) and volumetric fibroglandular fraction (VGF), defined as the proportion of FV relative to the total breast volume excluding the skin, in an objective manner. For diagnostic imaging, BCT has shown improved sensitivity over mammography and is US FDA-approved for diagnostic imaging. Efforts are ongoing to translate BCT for breast cancer screening.

OBJECTIVES:

To investigate the feasibility of using BCT to quantify FV and VGF in overweight/obese women.

METHODS:

In an ongoing cross-sectional study, 46/100 overweight/obese women, 40-65 years age, have been recruited. Anthropometric measures as well as 10-year and lifetime risks were obtained using IBIS risk estimator tool. Each participant underwent bilateral low-dose (4.01±1.17 mGy), non-contrast BCT to obtain reconstructed breast volumes at isotropic voxel size of $(0.218\ \text{mm})^3$ using FDK algorithm with appropriate weights. Each reconstructed breast volume was segmented and classified to provide the FV and VGF.[2] Feasibility will be evaluated by the proportion of measurable breast density within our study population.

RESULTS:

Interim analysis was conducted to determine feasibility. Quantitative breast density associated measures were obtained in all participants (100%; CI: 90-100%) evaluated by BCT, whereas measures were obtained in 110/151 (73%; CI: 65-80%) participants from the prior trial using MRI (35 could not fit the MRI scanner and 6 had technical issues), providing a significant improvement ($p<0.001$). Interim analysis also showed that after adjusting for age, BMI and waist circumference, increase in FV was associated with increased 10-year risk ($p=0.014$) and lifetime risk ($p=0.044$).

CONCLUSION:

Quantiative measures of FV and VGF is feasible using BCT in obese women. FV shows an association with 10-year and lifetime risks. Further studies are needed to determine if these measures can be used as endpoints to monitor response to preventive strategies.

What is the key finding new since 2019?

It is feasible to quantify FV and VGF in obese women using the newly-developed, low-dose, BCT that operates at screening radiation dose levels.

How does this finding impact screening strategies for women?

When BCT is translated for screening, FV & VGF can be obtained to enable risk-based screening.

ACKNOWLEDGMENTS:

Supported in part by NCI grants P30 CA023074 and R01 CA199044.

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UNRAVELLING THE CONTRIBUTION OF RISK, MASKING AND CANCER SIGNS MODELS TO THE SELECTION OF WOMEN FOR SUPPLEMENTAL IMAGING IN THE PROSPECTIVE SCREENTRUSTMRI TRIAL

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INTRODUCTION:

High breast density has been established as a risk factor for breast cancer and decreases the mammographic sensitivity. It has been shown that magnetic resonance imaging (MRI) has a higher sensitivity than mammography especially for women with dense breasts. The ScreenTrustMRI trial is a randomized clinical trial in a population-based mammography screening system at the Karolinska University Hospital in Stockholm, Sweden evaluating a measure based on artificial intelligence (AISmartDensity) to select women for supplemental MRI after negative screening mammography. Interim results have shown a cancer detection rate of 52 cancers per 1000 MRI examinations in the 'very high' category of AISmartDensity.

OBJECTIVES:

Our aim was to explore the contribution from each of the deep learning models for risk, masking and cancer signs that were combined to form the AISmartDensity score.

METHODS:

Inclusions of study participants started on April 1, 2021, and is planned to end before the same women return for their subsequent screening. Previously, we trained three AI models in-house for each specific task: risk for healthy women, mammographic masking and detecting cancer signs. For cancer signs, we summed the score of our in-house model with a commercial model from Lunit Inc. AISmartDensity is the sum of the standardized scores from each model, with the two cancer signs models together having the same weighting as each of risk and masking; plus an age adjustment. Among women not recalled after mammography screening, the women whose exams scored a 'very high' AISmartDensity score (>1.97 points, accounting for approximately 8% in a retrospective calibration) were invited to participate in the study. Upon accepting, they were randomized either to the intervention group having supplemental MRI screening or to the control group having no further examination. The results reported in this abstract refer to women included between April 1, 2021 and December 31, 2022.

Table 1. Algorithm scores (median; IQR)

	Invited	Completed MRI - Cancer	Completed MRI - No Cancer
AISmartDensity	2.36 (2.11- 2.77)	2.52 (2.18-3.05)	2.35 (2.08-2.79)
AISmartDensity w/o age compensation	3.27 (2.64-3.97)	3.90 (3.44-4.61)	3.28 (2.67-3.99)
Risk	1.15 (0.64-1.71)	1.53 (0.59-1.95)	1.18 (0.69-1.70)
Masking	1.06 (0.53-1.47)	0.87 (0.30-1.23)	1.07 (0.63-1.47)
Cancer signs	0.98 (0.45-1.83)	2.15 (0.96-3.13)	0.93 (0.39-1.81)

RESULTS:

Of all 52,675 mammography examinations analyzed, 3,610 (6.9%) women had 'very high' AI SmartDensity and were invited to participate. Of these, 1,316 (36%) women consented to participate in the trial and about half were randomized to MRI. A total of 536 women completed MRI. The median score for AISmartDensity was 2.36 (IQR: 2.11-2.77) and 2.52 (IQR: 2.18-3.05) for women invited and women diagnosed with cancer after MRI. The corresponding numbers for the standardized score for the risk model:1.15 (IQR: 0.64-1.71) and 1.53 (IQR; 0.59-1.95). The standardized score for the masking model: 1.06 (IQR: 0.53-1.47) and 0.87 (IQR: 0.30-1.23). The standardized score for the combined cancer signs models: 0.98 (IQR: 0.45-1.83) and 2.15 (IQR: 0.96-3.13).

CONCLUSION:

Overall, the contribution of each of the three model types was relatively equal in terms of selecting the 'very high' AISmartDensity group. However, the contribution to the actual cancers diagnosed, was highest for the combined cancer signs models and lowest for the masking model.

What is the key finding new since 2019?

In supplemental MRI combined cancer signs models contribute the most in the matter of cancers diagnosed, highlighting cancer signs models would lead to a increased cancer detection rate.

How does this finding impact screening strategies for women?

Emphasizing cancer signs models would lead to a more precise identification of women in need of supplemental MRI screening.

Current measures of mammographic density are more strongly associated with breast cancer risk in Asian post-menopausal compared to pre-menopausal women

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INTRODUCTION:

Mammographic density (MD) can be incorporated into risk prediction tools to improve the accuracy of risk stratification, and risk stratification approaches are currently being tested to improve the efficiency of screening. Several methods accurately measure MD, and each consistently shows strong associations with the risk of developing breast cancer[1]. However, given that Asian women are more likely to have dense breasts[2], it is unclear if MD measured by these methods that have largely been developed based on data in European women are predictive of breast cancer risk in Asian women.

OBJECTIVES:

We aim to evaluate the utility of MD in predicting breast cancer risk in Asian women. The specific objectives are:

(a) to determine the association of MD measured using area- and volume-based methods with risk of breast cancer
(b) to determine if these association are different by menopausal status.

METHODS:

Area-based MD measured using STRATUS and volume-based MD measured using Volpara were available for 2,284 (488 breast cancer cases, 1,796 controls) and 2,059 (436 cases, 1,623 controls) women of Asian ancestry, respectively. Controls were age- and ethnicity-matched to cases. The odds ratio (OR) of association between MD and breast cancer risk was estimated using conditional logistic regression, adjusted for potential confounding variables. For comparison between measurement methods, OR were standardized using OR per adjusted standard deviation (OPERA).

RESULTS:

All four MD phenotypes were significantly associated with breast cancer risk in Asian women in the combined analyses (Table 1). However, the stratified analyses showed that these associations were only significant in post-menopausal women, and the estimated OPERA were not significantly different than that reported in European women.

Table 1: Association of MD and breast cancer risk

MD	OPERA (p-value)		
	Overall	Pre-	Post-
DA	**1.19 (0.0008)**	1.08 (0.314)	**1.26 (0.0026)**
PDA	**1.23 (0.0002)**	1.13 (0.174)	**1.26 (0.0021)**
DV	**1.15 (0.0180)**	1.02 (0.737)	**1.25 (0.0170)**
PDV	**1.17 (0.0060)**	1.09 (0.337)	**1.22 (0.0140)**

DA/PDA: dense area and percent dense area; DV/PDV: dense volume and percent dense volume; pre-/post: pre and post-menopausal status.

CONCLUSION:

Our analysis suggests that MD measured using area- and volume-based methods can be considered as a potential biomarker in breast cancer risk prediction for post-menopausal Asian women. However, calibration of current mammographic estimation methods may be necessary to capture more accurate information in mammograms of Asian pre-menopausal women, especially those with smaller and denser breasts, to better predict their risk of developing breast cancer.

What is the key finding new since 2019?

MD measured using European-based methods are associated with breast cancer risk in Asian post-menopausal women but to a lesser extent in Asian pre-menopausal women.

How does this finding impact screening strategies for women?

Using MD in risk prediction tools to facilitate risk-stratified screening may be appropriate for Asian post-menopausal women. But these tools are likely to be less accurate in Asian pre-menopausal women.

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Association between premenopausal breast density and body composition

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INTRODUCTION:

Breast density is one of the strongest and most consistent risk factors for breast cancer. While body size is associated with breast density it only explains part of the association with breast cancer. Prior studies have used body mass index (BMI) to measure body size which does not take body composition or body fat distribution into account. To expand upon our prior work and more fully disentangle the relation between body size and breast density, we measured body composition and breast density with dual-energy X-ray absorptiometry (DXA). DXA has many advantages over BMI, including the ability to capture fat mass independent of lean mass as well as estimating visceral adipose tissue. Further, given that mammograms are not routinely taken until ages 40-45 prior studies may be missing a critical time period in understanding how body size and composition influence breast density.

OBJECTIVES:

To examine the associations between body fat distribution and body composition measures, and premenopausal breast density.

METHODS:

Study Population. Study participants were menstruating people ages 18 to 45 recruited from the Seattle metro area.

Breast density measurement. Breast density was measured using DXA scans. Total projected breast area was manually delineated on each image and breast fibroglandular volume (FGV; cm^3) and total breast volume (BV; cm^3) were estimated using a two-compartment model of adipose and fibroglandular tissue. Percent FGV was defined as the proportion of FGV relative to BV times 100. Percent breast density was examined as a linear variable and dichotomized at the median.

Body composition measurement. Body composition was measured with DXA. Automated software was used to segment visceral adipose tissue (VAT) from total abdominal fat as well as gynoid and android fat patterns. Body composition measures were included in the analysis as linear variables.

Statistical analysis. Pearson correlations were used to examine the associations between percent density and each body composition measure. Logistic regression estimated the odds of dense breasts for each unit increase in body composition measure.

RESULTS:

Fifty-six participants were included in this preliminary analysis. All body composition measures were inversely correlated with breast density with the strongest association with percent android fat (Table 1). In a model including android fat, gynoid fat, and BMI the odds ratio (OR) for being in top half of percent breast density by android (% fat) was 0.73 (95% CI=0.58-0.92) while neither of the other body composition measures (gynecoid fat or BMI) was significant.

Table 1. Pearson correlations between percent density and body composition measures (n=56)*

BMI	-0.68
Android	-0.87
Gynoid	-0.72
Android/Gynoid ratio	-0.80
VAT	-0.71

*All correlations significant at $p<0.0001$

CONCLUSION:

Body composition measures were associated with breast density, with the strongest association for an android fat pattern.

What is the key finding new since 2019?

To our knowledge no previous studies have examined the association between body composition measures and premenopausal breast density in a population of adult participants that have not reached recommended mammography screening ages.

How does this finding impact screening strategies for women?

Future research in this area might help define higher risk groups defined by body composition and breast density for alternative or targeted screening.

FUNDING: This work was supported by the Breast Cancer Research Foundation.

LONGITUDINAL ASSESSMENT OF ACTIVE AND PASSIVE DENSE MAMMOGRAPHIC TISSUE

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INTRODUCTION:

Markers detected through breast imaging can be effective in assisting with clinical decision-making. Detecting features that are indicators of breast cancer risk, such as the amount of fibroglandular tissue and parenchymal texture complexity, on mammography improves the accuracy of breast cancer risk prediction [1,2]. Alterations in breast tissue, such as an increase in mammographic breast density, signal changes in the tissue that could be indicative of benign breast disease or breast cancer and may be a result of elevated levels of collagen [3]. Stroma organization, including collagen structure, influences the dynamics of tumor invasion [4]. Although supplemental imaging allows for the visualization of stromal and glandular tissue to further assess risk, identifying and quantifying changes in regions of mammographic breast tissue that are restructuring [5,6], could provide further insights into tumor onset and progression.

OBJECTIVES:

Our goal was to identify areas of dense tissue that are restructuring (active tissue) and areas that remain passive and to quantify changes in breast composition over time.

METHODS:

Full-field digital mammograms were collected from sites in Maine, USA. Twenty-seven cases that were diagnosed with pathology-proven cancer within one year of the last screening were age-matched with 27 controls that were confirmed normal one year following the last screening. Mediolateral oblique (MLO) views from the tumorous breast (TB) and the contralateral breast (CB), along with the control right and left MLO views were analyzed using a sliding window approach to quantify the organization of tissue subregions of size 360 *pixels x* 360 *pixels* via the Hurst exponent (H) [5,6]. Subregions were classified into three categories, fatty tissue ($H<0.45$), active dense ($H\sim0.5$), and passive dense ($H>0.55$). Repeated measure analysis was performed to detect differences in the area (cm^2) of active and passive dense tissue over time.

RESULTS:

Regions of active and passive tissue were detected on mammograms (Figure 1). There were differences found between controls and cases for the area of both active and passive dense tissue (Table 1) with the differences in area of active tissue being more significant than passive dense tissue. The area changed in the left and right breasts over time for both controls and cases ($p<0.05$), but only the area of passive tissue for the contralateral breast for cases and controls varied significantly in rate (Table 1).

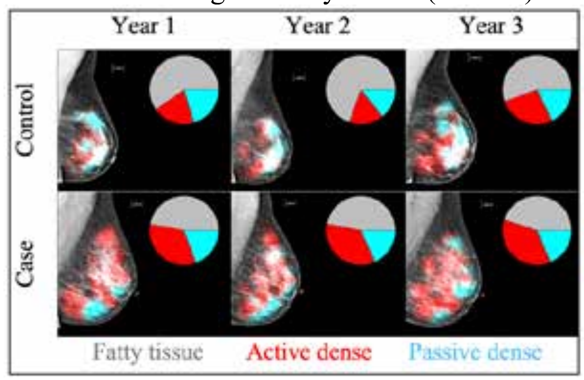

Figure 1. Passive dense tissue (blue) and active dense tissue (red) are highlighted on routine screening mammograms for a control patient (top row) and an age-matched cancer patient (bottom row).

Table 1. Repeated measures analysis *p*-values for differences in area and rates of change of passive vs active dense tissue.

	Passive tissue		Active tissue	
	TB vs. L_MLO	**CB vs. R_MLO**	**TB vs. L_MLO**	**CB vs. R_MLO**
Area	0.017	0.104	0.004	0.011
Rate	0.124	1.49e-06	0.538	0.455

CONCLUSION:

Differences and changes in active and passive dense tissue could provide further insights into cancer risk.

What is the new key finding since 2019?

Active and passive dense tissue can be quantified on mammogram screenings.

How does this finding impact screening strategies for women?

Implementing this approach into a new screening tool could identify patients who would benefit from medical intervention to reduce breast cancer risk.

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VOLUMETRIC PARENCHYMAL PATTERN ANALYSIS FOR BREAST CANCER RISK ESTIMATION

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INTRODUCTION:

Mammographic breast density is among the strongest breast cancer risk factors. Digital breast tomosynthesis (DBT) is quickly replacing 2D digital mammography (DM) and allows more detailed volumetric imaging of the breast. Radiomics, the high-throughput extraction of radiologic features, has enabled characterization of breast parenchymal complexity beyond breast density. In this study, we compare the performance of volumetric parenchymal pattern analysis from DBT and DM with conventional breast density measurement with respect to breast cancer risk estimation.

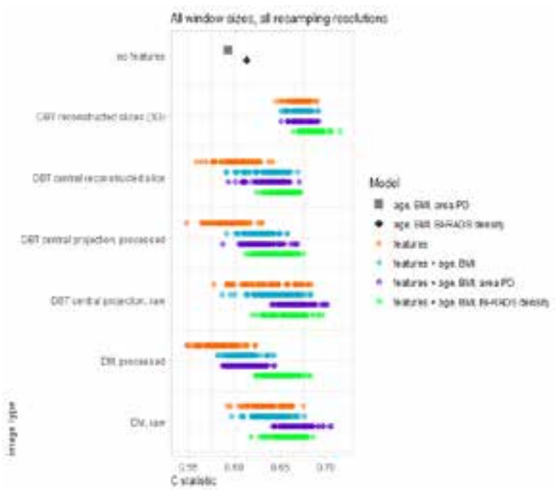

Figure 1. C-statistic for every window size × resampling resolution evaluated in our experimental settings, for each different image type and logistic model specification.

METHODS:

We performed a case control study in women with concurrent DM and DBT screening from 3/2011-12/2014. Cases were diagnosed with breast cancer within 1 year of screening; controls were confirmed negative or benign at 1 year follow-up, matched on race (Black, White, other/unknown) and age (5-year bins). Craniocaudal (CC) and mediolateral oblique (MLO) views for 187 cases and 737 controls, in six image formats were assessed: 1) raw DM; 2) processed DM; 3) raw DBT central projection; 4) processed DBT central projection; 5) DBT central reconstructed slice; and 6) DBT reconstructed stack. For cases, we analyzed the breast contralateral to cancer diagnosis, and the same breast in matched controls. We extracted 487 radiomic features using a lattice-based approach with the CaPTk[1] software, averaging features for each breast over CC and MLO views. We examined 3 lattice window sizes and 23 resolutions for image resampling. We performed principal component analysis for each combination and built conditional logistic regression models to assess the association of the first 7 principal components with breast cancer, with models including age, BMI, and BI-RADS density. We calculated the model C-statistic at all window sizes and resolutions (2304 experimental conditions).

RESULTS:

Features from reconstructed DBT scans had on average higher C-statistics across all experimental conditions. A model using only age, BMI, and BI-RADS density had a C-statistic of 0.61. Models using radiomic features plus age, BMI, and BI-RADS density had mean C-statistic of 0.68 (IQR 0.68, 0.69) for reconstructed DBT scans; for all other image types, the mean C-statistic ranged from 0.64 to 0.66.

CONCLUSION:

Incorporating 3D volumetric breast parenchymal patterns from DBT improves breast cancer risk estimation beyond markers derived from 2D DM and beyond conventional breast density metrics alone.

What is the key finding new since 2019?

Whole breast 3D parenchymal texture analysis is feasible in DBT, and preliminary evaluation suggest that fully 3D analysis can improve 2D measures and ultimately breast cancer risk assessment.

How does this finding impact screening strategies for women?

Adding of DBT to screening will improve breast cancer risk estimation beyond 2D DM.

Acknowledgements

This work was supported by the following grants: NIH/NCI R01CA161749 PI Kontos

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GROWTH AND DEVELOPMENT FACTORS RELATED TO MAMMOGRAPHIC DENSITY IN BLACK WOMEN

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INTRODUCTION:

High mammographic breast density is one of the strongest independent breast cancer risk factors and some studies have suggested that quantitative measures of mammographic density may be higher in Black women than in White women.[1] Reasons for these differences may reflect differences in the distribution of predictors of high mammographic density by race. Few studies, however, have described predictors of high mammographic density in Black women.

OBJECTIVES:

Identify growth and development characteristics, including body size at different ages and age at menarche, associated with mammographic density in Black women across the lifecourse.

METHODS:

Within the Black Women's Health Study (BWHS), a nationwide cohort of Black women, we used Cumulus to assess percent mammographic density (PMD) from digital screening mammograms for 5,882 women ages 40 – 74. We fit linear regression models to estimate β coefficients and 95% confidence intervals for the association of birth weight, childhood somatotype, age at menarche, body mass index (BMI) at age 18, adulthood height, BMI at mammography, and adulthood waist-to-hip ratio with PMD. Associations were evaluated overall and by age. We also performed a path analysis to assess the total, direct and indirect/mediation effects of the growth and development factors on age-adjusted PMD.

RESULTS:

The mean age at mammography was 56 and the average PMD for women <55 was 26% and 23% for women ≥55. The mean BMI of participants at age 18 was 21.4 kg/m^2 and 30.5 kg/m^2 at mammography. On regression analysis (Table 1), BMI at age 18, BMI at mammography, and adulthood waist-to-hip ratio were significantly and inversely associated with PMD. Results for women ages <55 and ≥55 were generally similar. Results of the path analysis supported these findings. The total effects of childhood somatotype, BMI at age 18, BMI at mammography, and adulthood waist-to-hip ratio strongly and significantly affected PMD.

Table 1: Associations of factors related to growth and development with PMD, 5,882.

Factors	PMD β (95% CI)
Birth weight (lbs)	-0.05 (-0.4, 0.3)
Childhood somatotype	-0.01 (-0.2, 0.2)
Age at menarche (years)	0.04 (-0.2, 0.2)
BMI at age 18 (kg/m^2)	-0.44 (-0.5, -0.4)*
Height (inches)	-0.10 (-0.2, 0.0)
Waist-to-hip ratio	-4.80 (-8.5, -1.2)*
BMI at mammography (kg/m^2)	-0.44 (-0.5, -0.4)*

All factors were modeled continuously. The model for BMI at age 18 was adjusted for age at mammography. All other models were adjusted for age and BMI at mammography. *p < 0.05

CONCLUSION:

Linear regression and path analyses suggest that across the lifecourse, greater childhood somatotype, BMI at age 18, BMI at mammography, and adulthood waist-to-hip ratio were significantly associated with lower adulthood PMD in Black women, with BMI at mammography and BMI at 18 being the strongest predictors.

What is the key finding new since 2019?

We report for the first time a comprehensive analysis of multiple metrics of body size across the lifecourse and quantitative measures of PMD in Black women. The few prior reports in Black women mainly relied on visual assessment of breast density or did not include earlier life measures.

How does this finding impact screening strategies for women?

Findings from this study provide unprecedented knowledge on predictors of high mammographic density in Black women and could help inform screening guidelines in this vulnerable population.

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ELEVATED NUMBERS OF TERMINAL DUCT LOBULAR UNITS IN THE NORMAL BREAST ARE ASSOCIATED WITH INFLAMMATION AND A UNIQUE IMMUNE LANDSCAPE

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INTRODUCTION:

Terminal duct lobular units (TDLUs) are epithelial structures in the breast that are the anatomical source of most breast cancers. TDLUs tend to involute (shrink) with increasing age, resulting in a reduction of the number and size of TDLUs[1]. Black women with[2] and without breast cancer[3] have been shown to have delayed TDLU involution in the normal breast (i.e., higher TDLU counts), which may be associated with elevated breast density[4] and the development of more aggressive breast cancer subtypes, including triple negative breast cancer[2], a particularly lethal disease which is more commonly diagnosed in Black women.

OBJECTIVES: In this study, we had two aims:
(1) To characterize molecular features of the normal breast in Black and White Komen Tissue Bank (KTB) participants, exploring potential morphometric, molecular, and immunological markers that may be related to breast cancer risk
(2) To better inform the etiologic processes that may occur early in breast carcinogenesis

METHODS: In a feasibility study, histologically normal fresh-frozen breast tissue was acquired from 47 Black and 47 White (n=94) premenopausal KTB donors undergoing voluntary research biopsies between 2009-2019. Average age was 39 years. The number of TDLUs in each biopsy tissue section was enumerated and dichotomized at the 75th percentile for all donors as low (<10) and high (≥10) TDLU count/mm^2 and linked with gene expression data from RNAseq.

We performed Ingenuity Pathway Analysis (IPA) to determine gene pathways associated with TDLU count. We also used CIBERSORT to estimate proportions of immune cell sub-populations by high or low TDLU counts.

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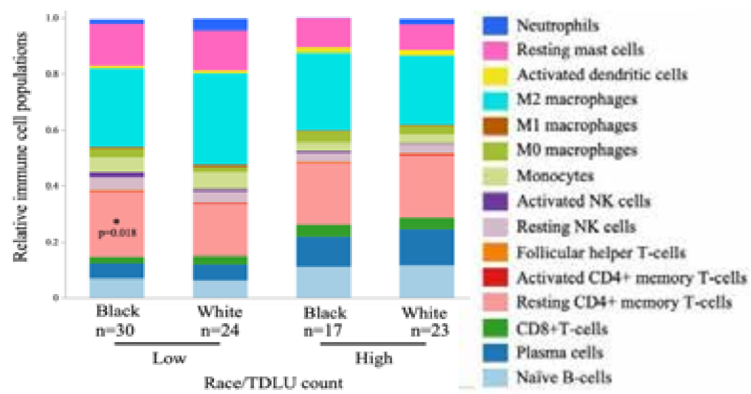
[4]Gierach, G.; et al. *J Natl Cancer Inst*. 2010 Oct 29

RESULTS:

Table. Top 3 canonical pathways associated with dichotomized TDLU counts/mm^2 in the normal breast from RNAseq gene expression data

Pathway	Function	p-value
eIF2 Signaling	Proinflammatory cytokine invasion	$2.64x10^{-35}$
Regulation of eIF4 and p70S6K Signaling	Translation regulation and initiation	$1.28x10^{-18}$
mTOR signaling	Cell proliferation, autophagy, and apoptosis	$2.46x10^{-13}$

Figure. Relative immune cell populations by low and high TDLU count/mm^2



CONCLUSION: Our results show that high TDLU counts/mm^2 in normal breast tissue are related to proinflammatory pathways and a unique immune microenvironment in Black women with low TDLU counts/mm^2 ($p = 0.018$).

What is the key finding new since 2019?
These findings suggest that reduced TDLU involution, a risk factor for breast cancer, may be associated with a proinflammatory immunological landscape in the normal breast.

How does this finding impact screening strategies for women?
Though preliminary, these findings suggest that immune mechanisms may play a key role in TDLU-related breast cancer risk, with potential implications for targeted screening and prevention strategies.

CHARACTERIZING THE IMMUNE MICROENVIRONMENT IN BENIGN AND CANCEROUS BREAST BIOPSY TISSUES IN RELATION TO MAMMOGRAPHIC DENSITY

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INTRODUCTION:

- Benign breast disease (BBD) is an independent risk factor for breast cancer, with 30% of invasive breast cancer cases estimated to have had a prior benign breast biopsy.
- Notably, radiologic density of the breast tissue in which the lesion develops has been found to modify the risk of progression to malignancy.
- However, the biological mechanisms underlying development of BBD, its interaction with breast density, and their joint influence on breast cancer risk remain unclear.

OBJECTIVE:

To understand the complex relationships between mammographic density and BBD biology through microenvironmental characterization of breast biopsies across the disease spectrum.

METHODS:

Study population: The Breast Radiology Evaluation and Study of Tissues (BREAST)-Stamp project is a molecular epidemiological study that enrolled women aged 40-65 years who underwent diagnostic, image-guided breast biopsy at the UVM Medical Center following an abnormal breast imaging exam between October 2007 and June 2010. Here, we demonstrate feasibility and present preliminary findings in an initial subset of participants across the following diagnostic subgroups: benign/non-proliferative (n=45), proliferative w/atypia (n=21), DCIS (n=17), LCIS (n=1), and invasive breast cancer (n=2).

Mammographic breast density (MBD) measurement: The single X-ray absorptiometry method[1] was used to quantify mammographic fibroglandular tissue volume using a density phantom (% FGV) in the biopsied breast, analyzed in tertiles based on its distribution among BBD patients.

Multiplex immunofluorescence (IF): Formalin-fixed, paraffin-embedded breast biopsy tissue sections underwent multiplex IF using a validated Ultivue panel (CD3, CD4, CD8, FOXP3, CD68, PD-1, PD-L1, pan-cytokeratin (CK)). Relative abundance of immune cell subpopulations (%/tissue area) were quantified in the stroma (CK-negative region).

RESULTS:

Figure. ***Multiplex immunofluorescence panel for phenotypic profiling of breast stromal microenvironment.***

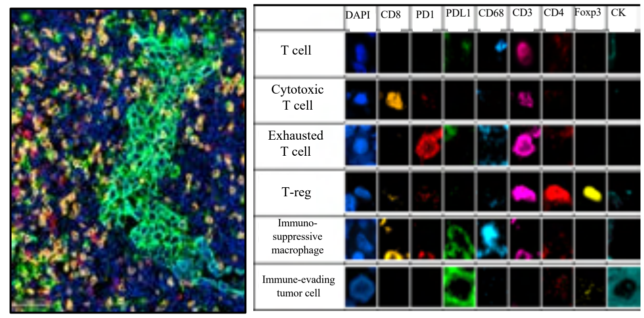

Table. ***Preliminary associations between % volumetric MBD and immune cell phenotype in BBD and cancer stroma (N=84).*** Multivariable linear regression model results for associations between MBD (low, medium, high) and each cell phenotype. Adjusted for age at biopsy (continuous), BMI (continuous), menopausal status (pre- or post-), a disease subtype (categorical). Pilot data are exploratory; thus, a p-value<0.2 will be used to generate hypotheses in larger cohort.

	BBD (n=64)				DCIS/Cancer (n=20)			
	Medium vs. Low MBD (ref)		High vs. Low MBD (ref)		Medium vs. Low MBD (ref)		High vs. Low MBD (ref)	
Cell Phenotype	β	p-value	β	p-value	β	p-value	β	p-value
T cells	-0.03	0.65	0.06	0.36	0.14	0.51	0.06	0.8
Helper T-Cells	0.01	0.97	0.46	0.23	1.1	0.28	0.38	0.75
Cytotoxic T-Cells	-0.03	0.64	0.07	0.38	0.29	0.4	0.22	0.59
Exhausted T-Cells	-0.001	0.96	0.05	0.07	0.08	0.2	-0.03	0.68
Cytotoxic Immune Cells	0.03	0.64	0.07	0.32	0.16	0.52	0.41	0.17
Regulatory T-Cells	0.07	0.55	-0.07	0.61	0.03	0.94	0.22	0.6
Foxp3+ T-cells	0.004	0.84	-0.03	0.2	-0.03	0.55	0.04	0.42
CD4/CD8 ++ T-Cells	-0.03	0.41	0.0007	0.96	0.37	0.33	0.04	0.93
Macrophages	1.83	0.06	1.16	0.28	-2.07	0.06	-0.49	0.69

In BBD, high MBD was associated with:
↑ exhausted T cells
↓ Foxp3 T cells
↑↑ macrophages

In cancerous tissues, high MBD was associated with:
↑ cytotoxic immune cells
↓↓ less macrophages

CONCLUSION & FUTURE DIRECTIONS:

This initial pilot study investigated the immune cellular microenvironment associated with breast density in a subset of the BREAST-Stamp study population. Future directions will include (1) increasing our sample size to allow for more in-depth subgroup comparisons by diagnostic group; (2) transcriptomic profiling using Nanostring; and (3) relating these findings to 10-year breast cancer risk.

What is the key finding new since 2019? Identifies factors in immune microenvironment of the stroma differentially associated with breast density in BBD and cancer.

How does this finding impact the field? Improves understanding of the cellular composition of fibroglandular tissue identified in radiologically dense areas on mammograms.

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RELATIONSHIPS BETWEEN AUTOMATED VOLUMETRIC LOCAL AND GLOBAL BREAST DENSITY ASSESSMENTS AMONG WOMEN UNDERGOING DIAGNOSTIC IMAGE-GUIDED BREAST BIOPSY

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INTRODUCTION:

Recent advances in breast density measurement tools have provided opportunities for automated and quantitative assessments of targeted areas of breast density across local regions of the breast.[1] However, the etiologic and clinical significance of local density regions has yet to be fully understood.[2]

OBJECTIVES:

We aimed to identify the densest regions within breast at a local level and explored whether women with the densest local regions as determined by Volpara™ Density Maps had the clinically densest breasts.

METHODS:

Analyses were conducted among 791 women aged 40-65 years undergoing clinically-indicated breast biopsy at the University of Vermont Medical Center. Local volumetric breast density from the 10 densest regions (square ROI with 10 mm side length; $\%VBD_{ROI\_X}$, X=1 (most dense) to X=10 (least dense)) was measured from Volpara™ Density Maps, and clinically used global volumetric breast density ($\%VBD_{GLOBAL}$) was estimated using TruDensity™ (Volpara Health Technology) from raw FFDM of the breast contralateral to biopsy. We examined Spearman rank correlation between $\%VBD_{ROI\_X}$ and $\%VBD_{GLOBAL}$.

RESULTS:

The mean (SD) age was 50.9 (7.0) years, mean BMI was 26.4 (6.2) kg/m^2, mean $\%VBD_{GLOBAL}$ was 11.4 (7.7)%, and mean %VBD of the most dense local region ($\%VBD_{ROI\_1}$) was 32.2 (14.3)%. The 10 densest local regions were all strongly and positively correlated with $\%VBD_{GLOBAL}$ in the same breast (P<0.0001) (**Table**). Findings suggested an increasing strength of associations with increasing severity of the biopsy diagnosis (**Table**). Local density also provided distinct information from global density e.g., 25% of women with low global Volpara Density Grade (VDG=a/b) had high $\%VBD_{ROI\_1}$ (≥15.5%) (**Figure**).

Table: Spearman rank correlations coefficients between local density of 10 densest regions and global density

Local density	Overall r	Benign/Non-proliferative r	Proliferative without atypia r	Proliferative with atypia r	DCIS or LCIS r	Invasive r
$\%VBD_{ROI\_1}$	0.89	0.89	0.88	0.94	0.84	0.92
$\%VBD_{ROI\_2}$	0.91	0.91	0.91	0.96	0.89	0.92
$\%VBD_{ROI\_3}$	0.92	0.92	0.91	0.95	0.91	0.93
$\%VBD_{ROI\_4}$	0.93	0.93	0.92	0.95	0.91	0.93
$\%VBD_{ROI\_5}$	0.93	0.93	0.92	0.95	0.93	0.93
$\%VBD_{ROI\_6}$	0.93	0.93	0.92	0.96	0.93	0.94
$\%VBD_{ROI\_7}$	0.93	0.93	0.92	0.96	0.93	0.94
$\%VBD_{ROI\_8}$	0.93	0.93	0.92	0.97	0.91	0.93
$\%VBD_{ROI\_9}$	0.93	0.93	0.92	0.97	0.91	0.93
$\%VBD_{ROI\_10}$	0.92	0.91	0.91	0.95	0.92	0.93

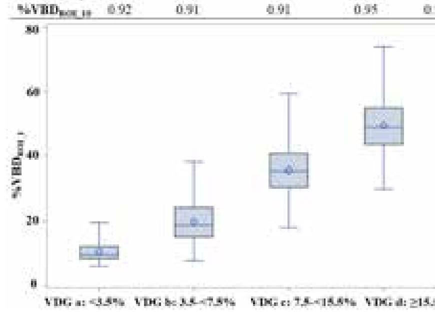

Figure. Boxplot of local density ($\%VBD_{ROI\_1}$) by global Volpara density grade (VDG a:<3.5%; b: 3.5-<7.5%; c: 7.5-<15.5%; d: ≥15.5%)

CONCLUSION:

Our findings suggest that local density may provide information beyond global density. Future work is needed to determine whether local density may work as a general and global marker of breast cancer risk.

What is the key finding new since 2019?

Automated Volpara™ Density Maps may provide new insights into within- and between-woman heterogeneity in density and density-associated breast cancer risk.

How does this finding impact screening strategies for women?

Regions of elevated local breast density may mask abnormalities in the breast; supplemental screening strategies may be needed, especially among women with discordant local density vs. global density.

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2. Otsuka M; Harkness EF; Chen X; et al. Local mammographic density as a predictor of breast cancer. Proc. SPIE 9414, Medical Imaging 2015: Computer-Aided Diagnosis, 941417 (20 March 2015).

Volumetric Breast Density: 2D vs 3D methods

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INTRODUCTION:

3D ultrasound tomography (UT) provides a quantitative estimate of speed of sound at mm resolution and a refraction corrected 360 compounded reflection image of connective tissue that is input to a bespoke 3D segmentation algorithm to yield a 3D volume of the fibroglandular tissue. The ratio of this volume to the total volume of the breast is volumetric breast density (VBD) and is important in Tyrer-Cuszik and other breast cancer models. Volpara is based on 2D projections but has developed efficient means to estimate VBD from mammograms.

OBJECTIVES:

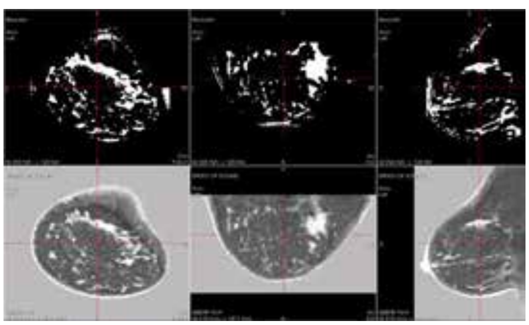


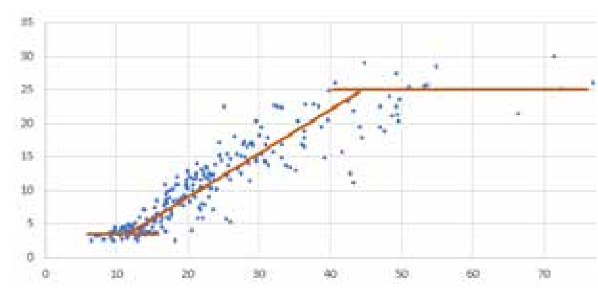
Figure 1. top: segmented volume of fibroglandular tissue. L to r: coronal, axial and sagittal view. bottom: speed of sound (SOS) QT Imaging ultrasound image: L to r: cor., ax., sag.

To verify that 3D ultrasound tomography (3D UT) or volography can accurately segment fibroglandular tissue in breast and compare QBD from 3D UT vs Volpara™.and MRI & establish nonlinear relationship between 2D vs 3D methods. We establish a nonlinear relation between QT 3D-UT and Volpara estimates by maximization of the cross-entropy function (log likelihood functional) and minimum squared error (MSE)

METHODS:

Data is collected on the QT Imaging 2000 Model A and segmented with a bespoke algorithm based on fuzzy c-means clustering (FCM) and thresholding[1]. 243 patients were scanned with the QT ultrasound scanner (3D UT) and a mammogram. The VBD was estimated with VolparaDensity™ and plotted against the VBD score from the 3D UT image. Curve fitting was based on a least squares regression and on maximum log likelihood. Spearman ρ was calculated and R for MSE to quadratic and logistic curves and linear regression for 40 cases MRI VBD.

RESULTS:



.Figure 2. Volpara density index vs QT VBD. Note the nonlinear nature of the relationship indicative of the 2D vs 3D origin of the respective indices.

The Spearman ρ = *.9332*, indicates monotonic relation, and a quadratic fit gives *R=0.9431*, indicating nonlinear relation. 3D MRI gives Pearson R=0.88 in linear regression with QT UT VBD.

CONCLUSION:

New logistic (nonlinear) correlation of 2D methods (Volpara) against 3D volumetric methods indicate the possibility of false identification of, or conversely, failure to identify, dense breasts using 2D projection based methods. Initial linear correlation of the MRI gold standard method of fibroglandular tissue estimation with QT UT based methods, high Spearman ρ, and two independent optimizations, support the validity of the 3D-UT based VBD.

What is the key finding new since 2019?

3D UT volumetric (not 2D) methods can avoid misclassification of breast or fatty breasts.

How does this finding impact screening strategies for women?

Accurate (sub-mm) VBD estimation is available with 3D-ultrasound tomography.

REFERENCES:

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STROMAL DISRUPTION ON HISTOLOGIC SECTIONS IMPAIRS TAMOXIFEN-ASSOCIATED MAMMOGRAPHIC DENSITY REDUCTION AND PORTENDS POOR PROGNOSIS IN ESTROGEN RECEPTOR-POSITIVE BREAST CANCER

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INTRODUCTION:

Mammographic breast density (MBD) reduction post-tamoxifen initiation is a favorable prognostic factor in estrogen receptor-positive (ER+) breast cancer and has potential utility as a biomarker of tamoxifen response. It is hypothesized that tamoxifen-associated declines in MBD may reflect breast stromal remodeling. However, stromal predictors of MBD reduction and, by implication, tamoxifen response have yet to be characterized using standard hematoxylin and eosin (H&E) staining.

METHODS:

Among ER-positive breast cancer patients aged 36-87 years treated with tamoxifen at Kaiser Permanente Northwest (1990-2008), we applied high-accuracy machine-learning algorithms to H&E-stained whole slide images from archival diagnostic breast tumor blocks to characterize stromal disruption phenotypes. Minimal, moderate, and substantial stromal disruption (**Figure 1**) were defined based on tissue features that are consistent with disruption of native stromal architecture, including reduction in dense (mostly collagenous) connective tissue stroma, and concomitant increases in stromal remodeling, stromal cellularity, desmoplasia, and necrosis.

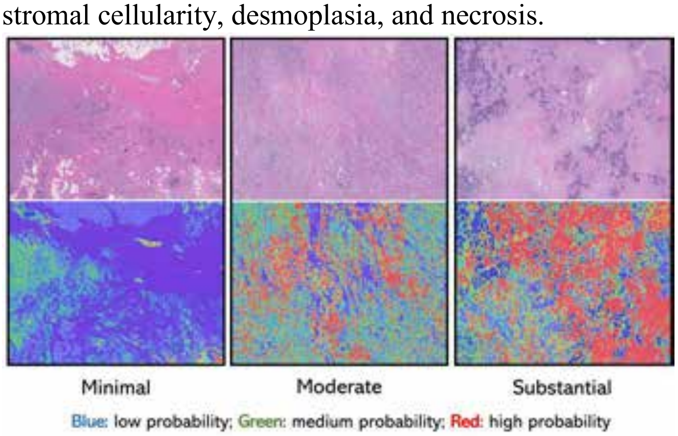

Figure 1: Morphology of stromal disruption in invasive breast cancer (Top panel: H&E images; Bottom panel: corresponding probability maps showing regions with varying probabilities of stromal disruption)

Among ER+ patients who died (cases; n=62) and did not die (controls; n=215) from breast cancer, we evaluated associations of stromal disruption with reduction in percent MBD in the unaffected breast measured pre- (mean=6 months) and post- (mean=12 months) tamoxifen initiation. Multivariable linear and logistic regression models were used to test associations of stromal disruption with MBD change and breast cancer-specific mortality (BCSM), respectively.

RESULTS:

Whereas baseline density was not associated with stromal disruption, the degree of MBD reduction (MBDΔ) after tamoxifen initiation differed by extent of stromal disruption. Compared with patients with minimal stromal disruption (mean MBDΔ = -7.10%), those with moderate (mean MBDΔ = -4.78%) and substantial (mean MBDΔ = -3.43%) stromal disruption had smaller MBD reductions even after accounting for standard clinicopathologic characteristics [$P_{\text{-trend}}$ = 0.004]. In case-control analyses, progressive stromal disruption was associated with worse BCSM, independently of standard clinicopathological characteristics [$OR_{\text{-trend}}$ (95% CI) = 2.06 (1.21-3.50); $P_{\text{-trend}}$ = 0.008]. In likelihood (LR) ratio tests, the combination of stromal disruption and MBD reduction provided prognostic information beyond standard pathological parameters alone ($\Delta LR\chi^2 = 8.23$; $P = 0.004$).

CONCLUSION:

Findings from this first report suggest that stromal disruption on tumor histologic sections might impair tamoxifen-associated MBD reduction and associated tamoxifen response in ER+ breast cancer patients.

What is the key finding since 2019?

We previously reported the prognostic value of tamoxifen-associated MBD reduction in this study population. Here, we extend the previous findings by showing that tamoxifen-associated MBD reduction might be impaired by or related to breast stromal characteristics.

What are the clinical implications of the findings?

Stromal disruption on diagnostic H&Es and MBD reduction could be used in conjunction to inform treatment decision-making and response for ER+ patients. Further studies are needed to characterize relationships between stromal characteristics, MBD reduction, and tamoxifen response in the preventive setting.

RELATION OF PRE- AND POST-DIAGNOSIS MEASURES OF MAMMOGRAPHIC BREAST DENSITY WITH CONTRALATERAL BREAST CANCER RISK AMONG BREAST CANCER SURVIVORS

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INTRODUCTION: Elevated mammographic breast density (MBD) is an established breast cancer risk factor; less is known about relationships between MBD and its changes with outcomes among breast cancer survivors. By 10 years post-breast cancer diagnosis, it is estimated that ~4% of patients will develop a second primary breast cancer in the contralateral breast. A growing body of literature suggests varying relationships between MBD and risk of contralateral breast cancer (CBC).

OBJECTIVES: We aimed to evaluate the role of MBD in relation to CBC risk among a cohort of breast cancer survivors and to determine whether risk associations varied by clinical characteristics.

METHODS: We conducted a nested case-control study within a retrospective cohort of 10,734 patients aged 20-85 years and diagnosed with a first primary unilateral invasive breast cancer (1990-2016) within US integrated healthcare systems (median follow-up=6.4 years). We evaluated the role of MBD in relation to CBC risk among 304 CBC cases diagnosed ≥1 year after the first (index) breast cancer and 597 controls at risk of CBC over the same time matched 2:1 on age, year, ER status, and stage of the index breast cancer. Percent (%) MBD was assessed in the contralateral breast using Cumulus at baseline (median=0.7 months before index breast cancer) and follow-up (median=11.6 months post-diagnosis). Odds ratios (ORs; 95% confidence intervals [CIs]) for the association of %MBD in categories (≤10, 10-30, and >30%) and CBC risk were estimated from logistic regression models adjusted for matching factors, body mass index, mammogram type (film/digital), and treatment (radiotherapy, chemotherapy, endocrine therapy).

RESULTS: Median time between index breast cancer and CBC diagnoses was 7.1 years. Baseline %MBD was associated with increased CBC risk ($OR_{>30\% vs. \leq 10\%}$=2.03, 95%CI: 1.13, 3.75; p-trend=0.015). Post-diagnosis %MBD was associated with over a 2.5-fold increased CBC risk ($OR_{>30\% vs. \leq 10\%}$=2.59, 95%CI: 1.56-4.31; p-trend<0.001); increased risk persisted for MBD ascertained closer in time (median=3.5 months) to CBC diagnosis and for patients whose index breast cancer was ER-positive. Elevated %MBD pre- and post-diagnosis was significantly associated with increased risk of CBC of a higher stage (II-IV) and grade (3/4) (**Table**).

Table: Multivariable multinomial logistic regression results for relation of %MBD* with CBC risk by tumor stage and grade

	Baseline %MBD		Follow-up %MBD	
Outcome	**OR***	**(95% CI)**	**OR***	**(95% CI)**
Stage of CBC				
Controls	1	Ref.	1	Ref.
Stage 0, I	1.1	(0.92, 1.20)	1.17	(0.98, 1.24)
Stage II, III, IV	**1.35**	**(1.02, 1.55)**	**1.38**	**(1.04, 1.48)**
Grade of CBC				
Controls	1	Ref.	1	Ref.
Grade 1 or 2	1.09	(0.91, 1.20)	1.12	(0.92, 1.20)
Grade 3 or 4	**1.29**	**(1.01, 1.44)**	**1.37**	**(1.09, 1.45)**

*OR per 10% increase in %MBD

A decline in %MBD of ≥5% from baseline to follow-up was associated with reduced CBC risk only among ER+ patients treated with tamoxifen (OR=0.45, 95%CI: 0.22, 0.93).

CONCLUSION: Our findings suggest the importance of both pre- and post-diagnosis MBD measures for CBC risk assessment among breast cancer survivors.

What is the key finding new since 2019? Elevated %MBD pre- and post-breast cancer diagnosis was significantly associated with increased risk of CBC of a higher stage (II-IV) and grade (3/4).

How does this finding impact screening strategies for women? The number of breast cancer survivors continues to increase with the growing, aging population and treatment advances. These findings underscore the importance of continued surveillance with potential supplemental screening modalities for women with elevated MBD to facilitate detection of CBC at an early stage.

Longitudinal Mammographic Breast Percent Density Changes for Breast Cancer Risk Estimation: Proof-of-concept study

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INTRODUCTION:

A recent study [1] showed that there is an increased risk of having breast cancer for women with a consecutive increase in their breast density. The previous study used only the four level BIRADS density classification, which may not capture the subtle temporal changes of women's breast density. Unlike BIRADS, breast percent density, the ratio of the dense tissue area and the entire breast area, can capture the subtle changes in breast density that may relate to breast cancer risk.

OBJECTIVES:

To determine the relationship between percent breast density and the risk of developing breast cancer.

METHODS:

We used a dataset of sequential screening mammography exams of 1,268 women from the University of Pittsburgh Medical Center. Each woman completed at least three annual exams. Among 1,268 women, 266 were in the high-risk group, as they had two negative mammograms and then had breast cancer identified at their third screening exam. The remaining 1,002 women were in the normal group with three consecutive negative mammograms. We extracted BIRADS density for each mammogram exam. For both groups, 60% had fatty breasts and the remaining 40% had dense breasts. We used our breast density segmentation algorithm [2] to segment the dense tissue area and the breast area of each mammogram view (i.e., R/L-CC, R/L-MLO). We then computed Percent Density (PD) using the equation,

$PD = Area(Dense) \, / \, Area(Entire\ Breast)$,

from each mammogram view. We averaged the PD of all four views to produce a PD for a given woman at that screening time point.

We used a linear mixed model accounting for correlation between the same women's exams (proc mixed, SAS, v.9.4, Cary NC) to assess possible trends (e.g., increasing/decreasing) over time in breast density measured by PD and BIRADS at three sequential annual screenings. We evaluated individual trends and compared them between the high-risk and normal groups.

RESULTS:

The average BI-RADS density scores demonstrated a consistent decreasing trend over the three years ($p<0.001$). The estimated decrease was slightly weaker for the high-risk group, without a statistically significant difference between the groups ($p=0.73$). In contrast, PD showed a substantial difference between the group-specific trends, estimates of which have non-overlapping confidence intervals supporting the statistically significant ($p=0.003$) difference (Table 1). We note that the confidence interval for the rate of PD change in the high-risk group includes negative values, indicating that a negative trend in this group is also not unlikely. These indicate the potential usefulness of the changes in PD as a marker of breast-density-related changes prior to cancer diagnosis.

Table 1: Trend in longitudinal density change between high-risk and normal groups

Average Slope	High-risk [95% CI]	Normal [95% CI]	p-value
PD	0.002 [− 0.002, 0.005]	− 0.004 [− 0.006, − 0.002]	0.003
BIRADS	− 0.021 [− 0.047, 0.006]	− 0.025 [− 0.040, − 0.013]	0.73

CONCLUSION:

Temporal changes in breast percent density may indicate breast-density-related changes precede cancer diagnosis, which can be difficult to identify using BIRADS scores. A more comprehensive study addressing the possible confounding factors should be implemented to validate the findings.

What is the key finding new since 2019?

Temporal changes in breast percent density may be more sensitive than BIRADS for breast-density-related markers of developing cancer.

How does this finding impact screening strategies for women?

If a woman's breast percent density decreases over time at a slower rate than expected, she may benefit from supplemental screening with MRI.

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1. Tran, TX et al. *Radiology*, 2022.
2. Lee, J & Nishikawa, RM. *Medical Physics 2018.*

MAMMOGRAPHIC DENSITY AND BREAST CANCER-SPECIFIC SURVIVAL IN THE BREAST CANCER ASSOCIATION CONSORTIUM

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*Presenting Author

INTRODUCTION: While prior studies have established that elevated mammographic breast density (MBD) is associated with diagnostic delays and increased risk of breast cancer and its recurrence, studies evaluating MBD as a possible predictor of breast cancer survival have yielded conflicting results. In the large population-based U.S. Breast Cancer Surveillance Consortium, we previously found in over 9,000 women that elevated MBD (assessed using the Breast Imaging Reporting and Data System (BI-RADS) density classification) was not associated with increased risk of death after accounting for patient and tumor characteristics.[1] Further, low MBD and high BMI have been related to worse breast cancer prognosis.[1, 2]

OBJECTIVES: We aimed to extend prior findings by determining the relation of quantitatively measured MBD with breast cancer-specific survival in the international Breast Cancer Association Consortium (BCAC).

METHODS: Analyses were based on 21 BCAC studies from 9 countries, comprising 6,539 women diagnosed with primary invasive breast cancer and followed for vital status. MBD measures were restricted to those obtained within 5 years of diagnosis, selecting the MBD measure that occurred closest in time to the diagnosis date (93% of patients) or if a pre-diagnostic mammogram was not available, then the MBD measure from the earliest mammogram within 1-year post-diagnosis (7% of patients). Percent MBD and absolute dense area (cm^2) were assessed using Cumulus, with results averaged across both breasts. Hazard ratios (HRs) and 95% CIs for the relation of MBD [standardized per 5% (%MBD) and $5cm^2$ (absolute dense area), and in quartiles] with breast cancer-specific survival were estimated using Cox proportional hazards regression with age as the time metric, adjusting for BMI at date of mammogram, ER status, HER2 status, tumor size, tumor grade, lymph node status, chemotherapy, endocrine therapy, radiotherapy, and calendar year of diagnosis.

REFERENCES:

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2. Strand F et al., Long-term prognostic implications of risk factors associated with tumor size…*Breast Cancer Res* 2018.

RESULTS: The 6,539 breast cancer patients accrued 59,774 person-years during an average (SD) follow-up of 9.1 (5.6) years; n=623 died from breast cancer. Elevated %MBD was associated with younger age, lower BMI, and diagnosis with tumors of larger size, higher grade, and positive lymph nodes (P<0.001). Compared with patients in the lowest %MBD quartile, patients in the highest %MBD quartile were at reduced risk of death from breast cancer before (HR=0.67, 95% CI: 0.52-0.87; P-trend=0.002) and after adjusting for patient and tumor characteristics (HR=0.73, 95% CI: 0.55-0.96; P-trend=0.025) (**Table**). Findings were similar in sensitivity analyses excluding 448 patients whose mammograms were post-diagnostic. No clear patterns of association were observed for absolute dense area.

Table: Multivariable survival model results for relation of MBD with risk of death from breast cancer, BCAC (n=6,539)

	HR (95% CI)	*P*
Percent density (%)*		
Q1: 0-<11.5	Ref	
Q2: 11.5-<23.9	0.85 (0.65, 1.10)	
Q3: 23.9-<39.9	0.82 (0.64, 1.04)	
Q4: 39.9-91.5	**0.73 (0.55, 0.96)**	
Per 5%	***0.97 (0.95, 1.00)***	***0.048***
Absolute dense area (cm2)*		
Q1: 0-<16	Ref	
Q2: 16-<31	0.96 (0.72, 1.28)	
Q3: 31-<52	**0.73 (0.58, 0.93)**	
Q4: 52+	0.87 (0.65, 1.16)	
Per 5 cm^2	*0.99 (0.98, 1.01)*	*0.40*

CONCLUSION: Among breast cancer patients, elevated %MBD was associated with reduced risk of death from breast cancer. It is biologically plausible that increased fat content within the breast may enhance obesity-related mechanisms that heighten tumor aggressiveness.

What is the key finding new since 2019?

Findings support a provocative duality of breast density's effects on risk and progression, with elevated %MBD increasing risk of breast cancer development but playing a lesser role in breast cancer-specific survival.

How does this finding impact screening strategies for women?

Findings from this international study underscore the need for improvements in screening sensitivity for earlier detection among women with dense breasts.

CAUSAL RELATIONSHIPS BETWEEN MAMMOGRAM RISK SCORES BASED ON TEXTURE AND DENSITY

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INTRODUCTION:

Mammogram risk scores based on texture (Cirrus) and density defined by different brightness thresholds (Cumulus, Altocumulus, and Cirrocumulus) are associated with breast cancer risk in different ways and could reveal different information about breast cancer risk. Whether there are causal relationships between the mammogram risk measures based on texture and density is unknown.

OBJECTIVES:

To understand the causal relationships between density-based mammographic measures defined by different brightness thresholds and a texture-based measure, Cirrus.

METHODS:

We digitized mammograms for 371 monozygotic twin pairs, none diagnosed with breast cancer at the time. We generated normalized, age-adjusted, and standardized risk scores for Cirrus, and for three spatially independent density measures, the light areas (Cumulus minus Altocumulus), the bright areas (Altocumulus minus Cirrocumulus) and the brightest areas (Cirrocumulus). Causal inference was made using the Inference about Causation from Examination of FAmilial CONfounding (ICE FALCON) methodology.

RESULTS:

The risk scores were correlated within twin pairs and with each other (r=0.22 to 0.81; all P<0.005). We estimated that 8-72% of the latter associations could be attributed to familial confounding between the risk scores with remainder attributed to causal relationships. There was consistent evidence for positive causal relationships: of Cirrus, the light areas, and the bright areas on the brightest areas (accounting for 34%, 55% and 85% of the associations); and of the light areas and bright areas on Cirrus (accounting for 37% and 28% of the associations).

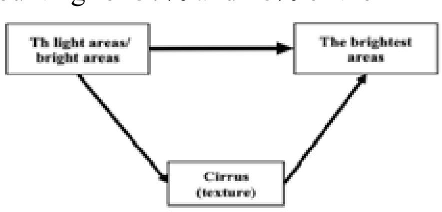

Figure 1. Diagrammatic representation of the inferred causal pathways between the Cirrus risk score and the risk scores based in the spatially independent mammographic density measures: light areas, bright areas, and brightest areas. Note: The thickness of the lines represents the relative strength of the inferred causal effects. For simplicity, the familial confounding between the pairs of risk scores is not shown in the diagram.

CONCLUSION:

The lighter (less dense) areas could be having a causal effect on the brightest (highly dense) areas, including a causal pathway through the mammogram risk score based on textural features. These findings would explain the consistent observations that the associations of Cumulus with breast cancer risk (including screen-detected, younger-age-at-diagnosis, and contralateral breast cancer) attenuate to the null after adjusting for Cirrocumulus and/or Cirrus; they could be due to, at least in part, the causal relationships between the less dense areas and the highly dense areas (and/or the texture-based measure). These findings also demonstrate how ICE FALCON can decompose associations between familial biomarkers into pathways.

What is the key finding new since 2019?

We are the first to investigate causal relationships between mammogram risk scores - based on texture and mammographic density defined by increasing brightness - by applying a novel approach for making inference about causation using twin pairs. In addition to familial confounding, we found evidence consistent with the lighter (less dense) areas having a causal effect on the brightest (highly dense) areas both directly, and through a mammogram risk score based on textures, Cirrus, which could be an intrinsic risk factor for breast cancer.

How does this finding impact screening strategies for women?

Cirrus, a texture-based mammographic measure could be integrated into risk prediction models to evaluate the risk of breast cancer. This may benefit young women who are not within the recommended age range for screening programs but are identified as high risk.

EXAMINING ASSOCIATIONS OF BREAST CANCER RISK FACTORS WITH VOLUMETRIC MEASURES OF BREAST DENSITY AT INCREASING THRESHOLDS AMONG WOMEN UNDERGOING DIAGNOSTIC IMAGE GUIDED BREAST BIOPSY

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INTRODUCTION:
Recent evidence suggests breast density (BD) determined at higher thresholds may improve breast cancer risk prediction.

OBJECTIVES:
The objective of this study was to examine strengths of risk factor associations with standard volumetric BD (VBD) measures and varying thresholds based on pixel-level VBD percent or fibroglandular tissue (FGT) thicknesses.

METHODS:
VBD was estimated from raw full-field digital mammographic images of breasts contralateral to a clinically-indicated biopsy using TruDensity™ (Volpara Health Technologies; ($VBD\%_{VOLPARA}$)) for 785 women, aged 40-65 years, at the University of Vermont Medical Center. $VBD\%_{VOLPARA}$ was recalculated from Volpara Density Maps™ after applying pixel-level thresholds of 5, 15 and 25% based on VBD% ($VBD\%_{VOLPARA\_5\%}$, $VBD\%_{VOLPARA\_15\%}$, $VBD\%_{VOLPARA\_25\%}$), or 5, 10 and 15mm based on FGT ($VBD\%_{VOLPARA\_5mm}$, $VBD\%_{VOLPARA\_10mm}$, $VBD\%_{VOLPARA\_15mm}$) (**Figure**). Pixels below these thresholds were considered to have no FGT. Linear regression models examined associations between breast cancer risk factors and square-root transformed VBD% measures, adjusted for age and body mass index (BMI).

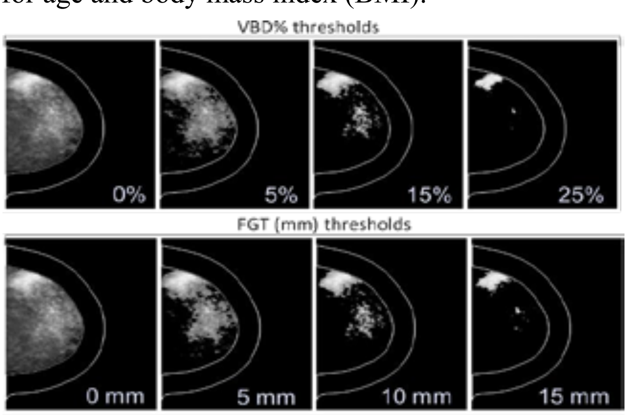

Figure. Representative examples of VBD thresholds.

RESULTS:
Among the study population, mean age was 50.9 (SD=6.9) years and BMI was 26.3 (SD=6.2) kg/m^2. Biopsy diagnoses included: benign/non-proliferative (33.6%), proliferative without (38.1%) and with atypia (6%), in situ (8.7%) and invasive breast cancer (13.6%). Mean $VBD\%_{VOLPARA}$ was 11.5% (SD=7.7). In general, similar patterns of association were observed for age, BMI, age at first birth, menopausal status and family history, with $VBD\%_{VOLPARA}$ and thresholded measures in expected directions. However, as thresholds increased, magnitudes of associations also tended to increase (**Table**).

Table. Association between biopsy diagnosis and volume density at increasing thresholds.

		Volumetric density (% threshold)								
		$VBD\%_{VOLPARA\_5\%}$			$VBD\%_{VOLPARA\_15\%}$			$VBD\%_{VOLPARA\_25\%}$		
Characteristic	N	β	SE	p-value	β	SE	p-value	β	SE	p-value
Pathologic diagnosis										
Benign/Non-proliferative	264	ref			ref			ref		
Proliferative without atypia	299	0.10	0.09	0.24	0.15	0.12	0.20	0.11	0.13	0.39
Proliferative with atypia	47	**0.62**	**0.16**	**0.0001**	**0.83**	**0.22**	**0.0002**	**0.94**	**0.25**	**0.0001**
in situ (LCIS or DCIS)	68	0.16	0.14	0.24	0.23	0.19	0.24	0.17	0.21	0.42
Invasive carcinoma	107	0.14	0.12	0.22	0.25	0.16	0.12	0.24	0.18	0.18
p-value for global test				**0.005**			**0.006**			**0.004**
p-value for trend				0.080			**0.045**			0.077

CONCLUSION:
Our findings of risk factor associations with thresholded VBD% suggest their potential for better extracting information contained in mammograms for understanding breast cancer etiology. Ongoing studies are investigating whether these thresholds are predictive of breast cancer risk.

What is the key finding since 2019?
Among women underdoing breast biopsy, thresholded breast density measures may inform etiology for determining future breast cancer risk.

How does this finding impact screening strategies for women?
Conducting these analyses provide an opportunity to learn at time screening about the heterogeneity of the densest tissue regions and to characterize an 'at risk' phenotype irrespective of the total breast density.

MULTISCALE ANISOTROPY ANALYSIS OF SECOND-HARMONIC GENERATION IMAGES OF BREAST TISSUE MICROENVIRONMENT

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INTRODUCTION:

The tumor microenvironment (TME) is characterized by a disorganization of the extracellular matrix. These restructuring changes may be detectable via computational mammography[1,2], but one can only infer that mammographic tissue disorganization is caused by TME alterations. We developed a wavelet-based technique to measure the multiscale anisotropy of collagen fibers from Second-Harmonic Generation (SHG) imaging[3,4] which demonstrates clinical cancer diagnostic potential and thus motivates its further exploration as a prognostic of breast cancer survival[5].

OBJECTIVES:

Our goal is to explore the multiscale anisotropic signature of SHG images of collagen fibers from breast TME and to establish a relationship with mammographic tissue disorganization[1,2].

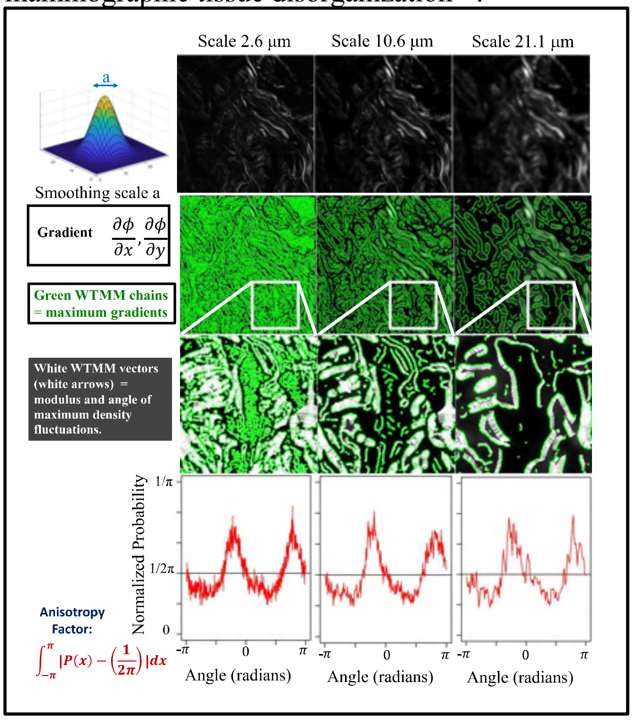

Figure 1. Description of the 2D WTMM anisotropy method. Three representative wavelet size scales are shown.

METHODS:

SHG-imaged biopsy slides from 10 Maine Medical Center patients (5 malignant, 5 benign) were analyzed using the 2D Wavelet Transform Modulus Maxima (WTMM) Anisotropy method[3,4] (Fig. 1). The analysis was done on 8 SHG images per patient slide.

RESULTS:

Four out of 5 malignant patients (resp. benign patients) are accurately classified by considering their small scale vs. large scale anisotropy factors (Fig. 2).

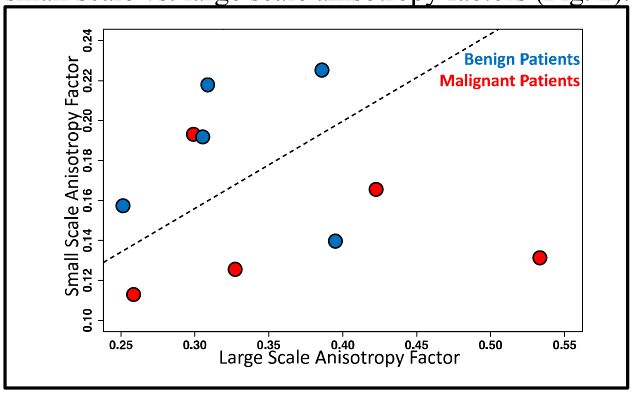

Figure 2. Small scale vs. large scale anisotropy factors for 5 malignant and 5 benign patients. The dotted line represents the split from 2 *k*-means clustering.

CONCLUSION:

Multiscale anisotropy from breast tissue SHG imaging may be a key cancer diagnostic candidate.

What is the new key finding since 2019? Studies investigating collagen directionality in breast TME are common[5,6], but none have explored the multiscale nature of anisotropic signatures. **How does this finding impact screening strategies for women?** Coupling computational mammography[1,2] with multiscale anisotropy analysis of SHG[3,4] may validate the prognostic power of combining both approaches in a clinical setting.

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EXTENDING THE BREAST CANCER SURVEILLANCE CONSORTIUM MODEL (BCSC) OF INVASIVE BREAST CANCER

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INTRODUCTION:

Breast cancer risk assessment is increasingly used to guide recommendations for breast cancer screening frequency, supplemental imaging, and prevention. We extended the Breast Cancer Surveillance Consortium (BCSC) version 2 (v2) model[1] of 5-year invasive breast cancer risk to include body mass index (BMI), 2nd degree family history of breast cancer, and age at first live birth (version 3 (v3)) to better inform appropriate breast cancer prevention therapies and risk-based screening.

OBJECTIVES:

To refine the BCSC model predicting invasive breast cancer by adding BMI, second degree family history of breast cancer, and age at first live birth to the earlier version of the model that includes age, race/ethnicity, 1st degree family history, history of benign breast biopsy and breast density.

METHODS:

We used Cox proportional hazards regression to estimate the age and race/ethnicity specific relative hazards for family history of breast cancer, breast density, history of benign breast biopsy, BMI, and age at first live birth for invasive breast cancer in the BCSC cohort. We evaluated calibration using the ratio of expected-to-observed (E/O) invasive breast cancers and discrimination using the area under the receiver operating characteristic curve (AUROC).

RESULTS:

We analyzed data from 1,455,493 women aged 35-79 years without a history of breast cancer. During a mean 7.3 years of follow-up, 30,266 women were diagnosed with invasive breast cancer. The BCSC v3 model had an E/O of 1.03 (95% CI 1.01-1.04) and an AUROC of 0.646 for 5-year risk. Compared with the v2 model, discrimination of the v3 model improved most in Asians, Whites and Blacks.

Among women with a BMI of 30.0-34.9 kg/m^2, the true-positive rate in women with an estimated 5-year risk of 3% or higher increased from 10.0% (v2) to 19.8% (v3), and the improvement was greater among women with a BMI ≥35 kg/m^2 (7.6% to 19.8%).

CONCLUSION:

The BCSC v3 model updates an already well calibrated and validated breast cancer risk assessment tool to include additional important risk factors. The inclusion of BMI was associated with the largest improvement in estimated risk for individual women.

What is the key finding new since 2019?

The addition of BMI, 2nd degree family history and age at first live birth improves discrimination of the BCSC risk assessment tool.

How does this finding impact screening strategies for women?

Breast cancer screening strategies are increasingly incorporating risk assessment into their recommendations for starting age of screening and interventions for prevention. Improvements in the BCSC model can advance recommendations for screening and prevention.

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AMINO ACID METABOLITES AND MAMMOGRAPHIC BREAST DENSITY IN PREMENOPAUSAL WOMEN

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INTRODUCTION:

A high mammographic breast density (MBD) is a strong risk factor for breast cancer, but the biological mechanisms explaining this relationship are not well understood. Certain amino acids are key for lipid and protein synthesis and may be essential for cell growth and proliferation. To the best of our knowledge, no study has investigated the association between amino acid metabolites and measures of MBD using an untargeted metabolomics approach.

OBJECTIVES: The objective of this study is to investigate the associations between amino acid metabolites and MBD in premenopausal women.

METHODS:

This study consists of 700 premenopausal women who were recruited during their annual screening mammogram at Washington University School of Medicine, St. Louis, MO, and provided a blood sample for metabolomics analyses. Untargeted metabolomic profiling, including 225 amino acids, was performed at Metabolon (Durham, NC). MBD was measured as volumetric percent density (VPD (%)), dense volume (DV (cm^3)), and non-dense volume (NDV (cm^3)), utilizing Volpara 1.5 (Volpara Health®). We performed multivariable linear regression models adjusting for age, age at menarche, body fat %, race, family history of breast cancer, oral contraceptive use, alcohol consumption, parity/age at first birth, and body shape at age 10 to assess the association between amino acid metabolites and measures of MBD. We calculated adjusted least square means (LSM) of MBD by quartiles of metabolites using multivariable linear regression and assessed for linear trend. Metabolites were standardized, and all MBD measures were $\log_{10}$ transformed to ensure normality of residuals. Coefficients were back-transformed to the original scale, and associations were considered significant if the FDR p-value <0.10.

RESULTS:

In multivariable linear regression analysis, two amino acids (glutamate and alpha-ketoglutaramate) were associated with VPD. One standard deviation (SD) increase in glutamate was associated with a 10% decrease in VPD (FDR p=0.001), while one SD increase in alpha-ketoglutaramate was associated with a 9% increase in VPD (FDR p=0.05). In LSM analysis, VPD decreased across quartiles of glutamate levels: (Q1= 9.8%, Q2=8.5%, Q3=8.4%, Q4=7.4 %, FDR p-trend=0.005) and increased across quartiles of picolinate (Q1=7.8%, Q2=8.6%, Q3=8.3%, Q4=9.7%, FDR p-trend=0.06).
Three metabolites were positively associated with NDV. One SD increase in glutamate was associated with an 8% increase in NDV (FDR p=0.04), and a SD increase in aspartate and cysteinylglycine disulfide, was associated with a 7% increase in NDV (FDR p=0.05). NDV increased across quartiles glutamate (Q1=715.2 cm^3, Q2=796.2 cm^3, Q3=808.2 cm^3, Q4=893.9 cm^3; FDR p-trend=0.03) and, hydroxyasparagine (Q1=716.7cm^3, Q2=791.5 cm^3, Q3=839.2 cm^3, Q4=885.1 cm^3; FDR p-trend=0.08). There were no associations between amino acid metabolites and DV.

CONCLUSION:

Using untargeted metabolomics, we identify, for the first time, amino acid metabolites that are associated with VPD and NDV in premenopausal women. Additional studies are needed to confirm our findings, understand the potential underlying mechanisms and how this may influence risk of breast cancer.

What is the key finding new since 2019?

The associations of glutamate with both VPD and NDV makes it a biomarker of interest in MBD.

How does this finding impact screening strategies for women?

Identification of amino acid metabolites associated with MBD may provide insight about the biological mechanisms underlying MBD and potentially breast cancer risk.

ADDRESSING CLASS IMBALANCE AND OVERCONFIDENCE OF U-NET SEGMENTATION MODELS FOR DENSITY AND RISK ASSESSMENT

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INTRODUCTION:

Multiclass segmentation often confronts problems of class imbalance for training networks with medical images.[1] In breast images, the number of instances or classes used to determine risk of cancer or masking can impact the performance of machine learning algorithms.[2]

OBJECTIVES:

Post-hoc Dirichlet calibration[3] (DC) is proposed to improve the probability predictions of multiclass U-Net models used for breast density and risk assessment.

METHODS:

A virtual clinical trial (VCT) method was used to simulate breast phantoms (n=264) that represent the complex structures of mammary parenchyma.[2] Lesions composed of soft tissue were embedded into the parenchyma, and projections were simulated following the settings of a tomosynthesis system.[2] The ground-truth mask of the projections (maximum intensity projection or MIP) were mapped into the following risk areas: class 0 (background) and classes 1 to 3 (composition predominantly of adipose, dense, and lesion tissues). Notably, instances of class 3 were significantly lower than the others, requiring methods to address class-imbalanced data during training of networks.

The central unprocessed projections were resized (360×600) and used as input to train a U-Net for risk segmentation. The proportion of images used for training, validation, calibration, and testing was 168:24:24:48. We performed parametric sweeps to optimize the U-Net hyperparameters. Our previous work[2] shows predictions with increased false positives for class 3, characterizing overconfidence in the risk segmentations.[3]

DC was used to adjust the model's output probabilities. DC provides a calibration map ($\hat{\mu}$) using a vector of class probabilities; softmax on a linear function of an input probability vector (q)**,** parametrized by matrix (W) and bias vector (b): $\hat{\mu}\,(q, W, b) = \sigma(W \ln q + b)$; $\hat{\mu}$ is applied to the vectors of probabilities produced by the multiclass models to reduce overconfidence and false positive predictions.

RESULTS:

Before DC, the model resulted in the values (0.89, 0.82, 0.28) and (0.89, 0.86, 0.17) for Dice and Precision (classes 1, 2, 3), respectively. After DC, the model resulted in the values (0.90, 0.85, 0.43) and (0.89, 0.86, 0.50) for Dice and Precision (classes 1, 2, 3), respectively. The simulations show improvement in the $\hat{\mu}$ (Figure 1B), especially for the class risk 3 (Figure 2D).

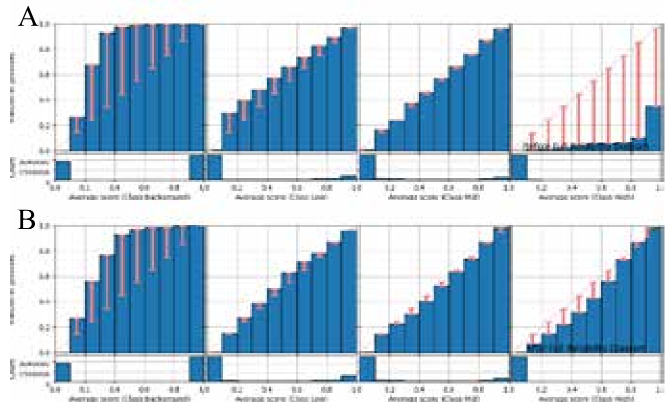

Figure 1. Reliability diagrams (A) before and (B) after DC for risk segmentation of (left to right) classes 0, 1, 2, and 3, respectively.

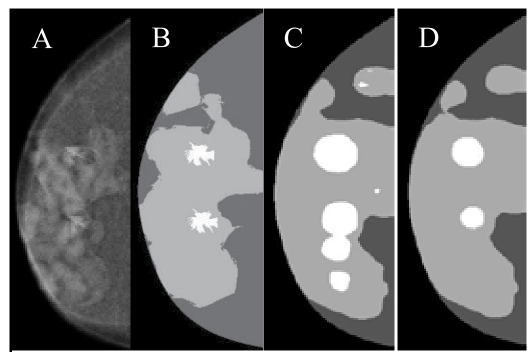

Figure 2. (A) Central projection (enhanced with imaging processing), (B) MIP (ground truth), predictions (C) before, and (D) after DC.

CONCLUSION:

DC improved the performance of multiclass segmentation model explored in this work (**key finding**). Our simulation-based models will be modified to improve breast cancer risk assessment in patient images (**impact in screening strategies**).

ACKNOWLEDGEMENTS: Support was provided by the Terri Brodeur Breast Cancer Foundation, American Association of Physicists in Medicine (2020 Research Seed Funding Grant), Breast Cancer Alliance, Inc. (2022 Young Investigator grant), DoD (W81XWH-18-1-0082), Burroughs Wellcome Fund (IRSA 1016451), and NIH (P30CA016520). ADAM is the spouse of a shareholder of Real Time Tomography (RTT) and a member of the scientific advisory board of RTT. ADAM has received equipment support from Analogic Inc, Barco NV, and RTT. We thank Dr. Hilde Bosmans for providing the models of spiculated masses used in this work.

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Assessing Improvements in Dense Tissue Visualization in Next-Generation Tomosynthesis Through Mastectomy Specimen Imaging

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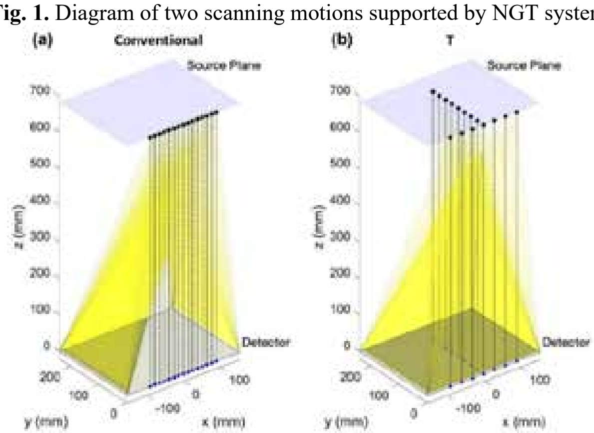
INTRODUCTION: Digital breast tomosynthesis (DBT) is now in widespread use for breast cancer screening. In current clinical systems, the x-ray tube scans along the chest wall [Fig. 1(a)], creating a cone-beam artifact in the perpendicular direction (posteroanteriorly). We have built a next-generation tomosynthesis (NGT) system which can scan in both the left-right and posteroanterior directions, forming a "T" [Fig. 1(b)]. In phantoms, this design yields more isotropic in-plane resolution, fewer cone-beam artifacts, and better *z*-axis resolution.[1]

Fig. 1. Diagram of two scanning motions supported by NGT system.

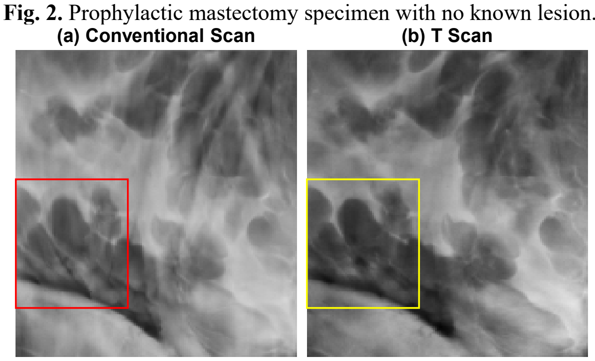


OBJECTIVES: To understand how the T scan would impact dense tissue visualization, two mastectomy specimens with no known lesion were imaged. To expand our prior work[2], anatomical noise and high-order texture are calculated in this abstract. These are surrogate metrics for assessing detectability and tissue superposition effects.

METHODS: Burgess showed that anatomical noise in breast imaging follows a power-law function: $\kappa \cdot f^{-\beta}$, where κ is an amplitude term, f is radial frequency, and β is the power-law exponent.[3] Burgess hypothesized that β is a surrogate metric for detectability, with lower values of β indicating higher detectability. To calculate power-law noise, five centrally-located slices in the reconstruction (corresponding to 5 cm of breast thickness) were analyzed. We used a sliding window (size 128 × 128) to maximize the number of regions-of-interest (ROIs) for sampling. ROIs that contained zeros (air) were excluded.

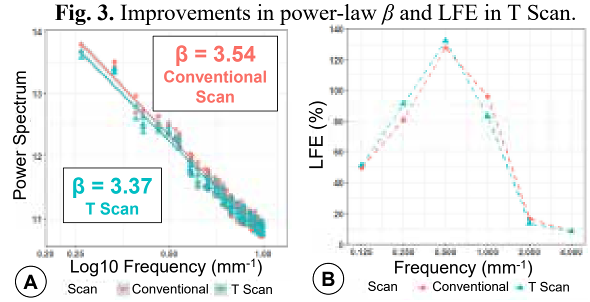
We also calculated Laplacian Fractional Entropy (LFE) proposed by Abbey *et al.* to evaluate high-order breast texture using ROIs convolved with Gabor kernels over six orientations (0° to 150° in 30° increments).[4] The Gabor-filter response histogram was analyzed in terms of entropy, and the relative entropy of the best-fit Gaussian distribution was then normalized to the best-fit Laplacian distribution to calculate LFE. Abbey *et al.* observed that low-frequency LFE is a surrogate measure of tissue superposition effects, with higher LFE indicating fewer tissue superposition effects and thus better image quality.[4]

Fig. 2. Prophylactic mastectomy specimen with no known lesion.



RESULTS: As shown in one of the specimens, dense-adipose tissue separations are clearer in the T scan (Fig. 2). We found that power-law β in the T scan (3.37) is lower than the conventional scan (3.54), offering data in support of superior detectability [Fig. 3(a)]. Additionally, we have preliminary data that LFE is indeed higher in the T scan at frequencies [0.125, 0.50] in mm^{-1}, mitigating tissue superposition effects [Fig. 3(b)].

Fig. 3. Improvements in power-law β and LFE in T Scan.



CONCLUSION: In specimen image analyses, metrics of dense tissue visualization are improved by the T scan.

What is the key finding new since 2019? This is a new project that we started after the 2019 conference.

How does this finding impact screening strategies for women? The T scan is a design refinement that we aim to analyze with human subjects (recruiting later this year).

ACKNOWLEDGEMENTS: Support was provided by Breast Cancer Alliance, Inc. (2022 Young Investigator grant), DoD (W81XWH-18-1-0082), Susan G. Komen® (PDF14302589 and IIR13264610), Burroughs Wellcome Fund (IRSA 1016451), NIH (T32EB009384, R01CA196528, R37CA273959, P30CA016520, and UL1TR001878), and in part by the Institute for Translational Medicine and Therapeutics (ITMAT) Transdisciplinary Program in Translational Medicine and Therapeutics at UPenn. A.D.A.M. and R.J.A. are inventors on patents and patent applications related to the NGT technology. A.D.A.M. is the spouse of a shareholder of Real Time Tomography (RTT) and a member of the scientific advisory board of RTT. Equipment support was provided by Analogic Inc., Barco NV, and RTT. We thank RTT for help with reconstructions.

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INTERPLAY BETWEEN GENETIC AND NON-GENETIC FACTORS INFLUENCING MAMMOGRAPHIC DENSITY

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INTRODUCTION:

Studies have identified genetic and non-genetic factors associated with mammographic density (MD). However, known MD-associated genetic variants only account for a small proportion of total estimated heritability. Interrogating relationships between genetic and non-genetic factors could identify additional MD-associated loci, expand understanding of the genetic basis of MD risk, and clarify how non-genetic factors may modulate relationships between genetic variants and MD.

OBJECTIVE:

To identify statistical interactions between genetic variants and non-genetic factors associated with MD phenotypes.

METHODS:

All analyses are based on European ancestry women included in Breast Cancer Association Consortium (BCAC) studies with available mammographic density phenotypes, genetic and non-genetic data (N = 5,918 – 9,349 depending on specific analyses). We conducted six separate genome-wide gene-environment (GxE) interaction scans using body mass index (BMI) and parity assessed near the time of mammogram as the non-genetic factors and three MD phenotypes (percent density (PD), dense area (DA), and non-dense area (NDA)). Outcome measures were square root transformed and normalized. We used 351,788 genotyped variants (Illumina OncoArray) with minor allele frequency > 5% that passed standard QC filters. All models were adjusted for age at mammogram, BCAC study, and 10 genetic principal components. We conducted 1df GxE interaction tests using a Bonferroni-corrected significance threshold of $p < 1.42\times10^{-7}$ (0.05/351,788). Future analyses will include imputed genotype data (imputed to 1000 Genomes Project) and additional non-genetic factors (height, menopausal hormone therapy, and breastfeeding) from a larger set of BCAC women (Table 1).

RESULTS:

All non-genetic factors showed association ($p < 0.05$) with at least one MD phenotype. For BMI and parity, we observed no significant interaction effects for any of the three MD phenotypes at our Bonferroni-corrected threshold.

CONCLUSION:

To our knowledge, this is the largest study to assess the interplay between non-genetic and genetic factors in relation to MD phenotypes. We are in the process of adding additional samples and genetic variants to enrich our analyses. These results will increase our understanding of the interplay between genetic and non-genetic factors to influence mammographic density.

Table 1. Approximate sample sizes for planned GxE interaction analyses, by non-genetic factor and MD phenotype

Non-genetic factor	PD	DA	NDA
Body mass index	18,631	16,189	16,188
Height	17,538	15,000	14,999
Parity	18,262	15,918	15,917
Menopausal hormone therapy	11,894	10,083	10,083
Breastfeeding	12,983	12,930	12,929

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CHARACTERIZING THE EFFECTS OF ANTI-INFLAMMATORY DRUG SULINDAC ON THE EXTRACELLULAR MATRIX PROTEINS OF BREAST TISSUE

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INTRODUCTION: In population studies, regular use of non-steroidal anti-inflammatory drugs (NSAID) that inhibit cyclooxygenase 2 is associated with a reduced risk of breast cancer and, in some studies, lower breast density; a risk factor for breast cancer. In mouse mammary tumor models, cyclooxygenase-2 (COX2) modulates tumor development in collagen-dense microenvironments and the inhibition of COX-2 inhibition reduces collagen deposition. We reported (Thompson et al., Clin Cancer Res. 2021 Oct 15;27(20):5660-5668) that use of the NSAID sulindac in a clinical trial reduced breast density and decreased tissue collagen fiber straightness, a hypothesized protumor feature of collagen, in postmenopausal women. We will report our findings on sulindac use and breast tissue collagen composition in postmenopausal women and relate peptide changes to breast density and collagen physical properties of length, width, and straightness.

OBJECTIVES: In postmenopausal women with a history of early-stage breast cancer on aromatase inhibitor therapy with an unaffected contralateral breast treated for 6 months with 150 mg sulindac twice daily,

- Assess change in breast tissue collagen peptide composition and
- Relate change in breast tissue collagen peptide composition to breast density and to collagen fiber length, width and straightness.

METHODS: To examine the effect of COX2 inhibition on breast tissue collagen, breast core needle biopsies were obtained during a single arm trial of the NSAID sulindac (150 mg bid) studied for effect on tissue biomarkers. A total of 50 postmenopausal women with a history of hormone eceptor positive breast cancer taking adjuvant aromatase inhibitor therapy initiated sulindac. At completion, 36 agreed to undergo biopsy of the unaffected, contralateral breast at baseline and 32 had sufficient tissue for paired analyses of treatment effects. Analysis of tissue collagen-associated peptides (*i.e.,* COL1A1, COL1A2, COL3A1, COL6A) was conducted using whole slide tissue imaging mass spectrometry proteomics. For this report, individual peptide signals were normalized to total ion current and mean peak intensity per area across the entire biological specimen was used to report a score for each patient. Integrated hypothesis testing was performed and differentially expressed peaks (DEPs) with false discovery rate (FDR) <0.05 and log2 fold-change >0.58 were selected for further examination. Unsupervised hierarchical clustering and heatmap visualization were used to assess differential expression of the peaks.

RESULTS: Following MALDI-MS, ~550 peptide peaks were identified. Of these, 106 collagen related peptides are being studied. A high degree of interindividual variability has been observed between peaks. The use of integrated hypothesis testing (feature extraction) identified 10 DEPs (2 down/8 up) with sulindac. Peptide identification studies support alterations in posttranslational modifications in COL1A1, COL3A1, COL6A3 and COL6A2 indicating drug activity on the enzymatic activity of prolyl hydroxylases. Four peptides are currently unknown. Exploratory analyses indicate the change in the individual DEPs with sulindac are dependent on pre-peptide levels and on body mass index but not time on aromatase inhibitor, baseline breast density, age, or aspirin use. *Analyses are ongoing for relation to collagen fiber features.*

CONCLUSION: Six-month treatment with sulindac is associated with specific changes in collagen-associated peptide peaks supporting an effect of NSAIDs on collagen-associated peptides in breast tissue. Ongoing peptide sequencing and whole slide cell profiling will inform on the biological relevance of these findings including hypothesized effects of NSAIDs on prolyl hydroxylase enzymes and posttranslational modification of collagen.

What is the key finding new since 2019?

Our key findings are evidence that sulindac treatment reduces breast density and that this may be through effects on tissue collagen structure that may be mediated through effects on prolyl hydroxylases.

How does this finding impact screening strategies for women? Our findings do not have an immediate impact on screening though we imagine a better understanding of the biochemical basis of breast density will ultimately inform on risk, risk biomarkers, and guide new screening strategies.

3D ultrasound tomography volumetric breast density: comparison of methods

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INTRODUCTION:

3D ultrasound tomography (3D UT) gives high resolution (sub-mm) speed of sound (SOS) and refraction corrected reflection images. We have established the accuracy of bespoke segmentation algorithms to estimate the fibroglandular tissue volume (FTV)[1] and volumetric breast density (VBD) which is used in Tyrer-Cuzik models. We show the equivalence of variants of the algorithm with and without reflection images.

OBJECTIVES:

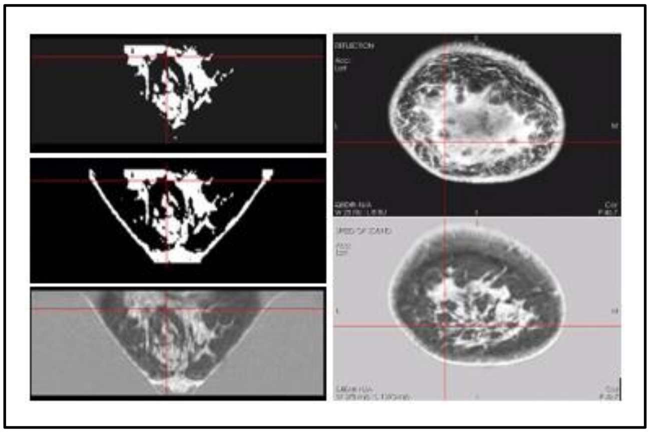

Figure 1. left: top to bottom: fibroglandular tissue (FGV), FGV w/ skin & speed of sound. Right: top refraction corrected reflection image bottom: speed of sound image.

To verify that 3D UT or volography can accurately segment fibroglandular tissue in breast without reflection images and with either thresholding based (TB) or fuzzy C-means (FCM) methods.

METHODS:

Data is collected on the QT Imaging 2000 Model A and segmented with the algorithm based on fuzzy c-means clustering (FCM) and thresholding[1] with and without reflection and the VBD was compared with Volpara™ densities and the non-parametric *Spearman* ρ's were calculated & compared.

RESULTS:

Using reflection images slightly increases Spearman ρ, decluttering does not improve ρ, smoothing slightly increases ρ. The Pearson correlation between FCM vs TB methods is 0.988 indicating strong linear correlation and equivalence. The Spearman ρ are shown in Table 1 showing monotonic relationships.

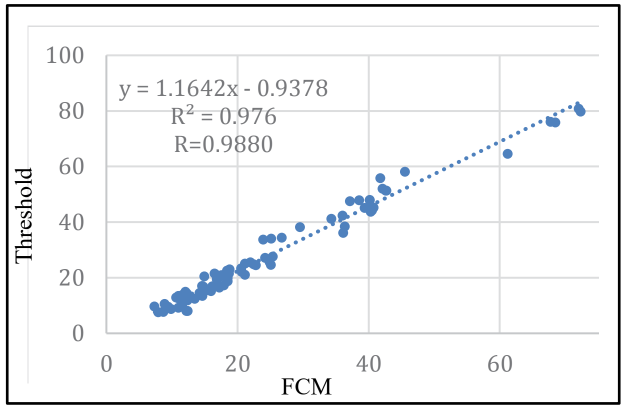

Figure 2. Scatterplot of Thresholding vs FCM methods for determining FGV. The Pearson R is 0.988.

Speed, attenuation, reflection: decluttered	**0.93**
Speed, attenuation, reflection: no declutter	0.93
Speed and attenuation, with smoothing	0.95
Speed and attenuation, no smoothing	0.915

Table 1: Spearman ρ is calculated for rank of various QT VBD algorithms against rank of Volpara™.

CONCLUSION:

Different methods for calculation of the FGV and VBD, all based on 3D-UT, are shown to be highly correlated and have high Spearman ρ with Volpara density, indicating validity of the 3D-UT method.

What is the key finding new since 2019?

The equivalence of different methods based on 3D-UT, and rank correlation with Volpara™.

How does this finding impact screening strategies for women?

Accurate estimation of volumetric breast density is relevant to breast cancer risk[2, 3] and available with 3D-UT and concomitant VBD algorithm.

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Image-Based Models for Predicting Advanced Breast Cancer Risk

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INTRODUCTION:

Advanced breast cancer is associated with increased mortality and poorer survival outcomes[1]. Previous work showed that proliferative atypia, obesity, and high breast density are associated with advanced stage cancer risk[2]. Mammography plays an integral part in overall risk evaluation yet, imaging signals other than breast density, associated with advanced stage cancer risk are underexplored.

OBJECTIVES:

The purpose of this study is to investigate imaging signals related to advance stage cancer risk.

METHODS:

Full field digital mammograms (FFDM) were provided by the Hawai'i and Pacific Islands Mammography Registry (NIH R01CA263491 and U54CA143728) and cancer status was provided by the Hawaii Tumor Registry. Advanced stage was defined as anatomical stage IIB or higher or having a pathological stage II or higher according to AJCC guidelines. The non-advanced stage cancer comparison group was comprised of early stage cases and cancer-free women. Clinical breast density and a deep learning (DL) derived density was also exported with each FFDM.

Five-fold cross-validation was used to simultaneously train and validate 5 logistic regression models to classify advanced cancer or non-advanced cancer. Models differed by input which included clinical density, DL density, image features, combined clinical density and image features, and combined DL density and image features. DenseNet121, pretrained with ImageNet weights, was used to derive 1024 imaging features for each FFDM. All models were age adjusted except the image feature model.

RESULTS:

A total of 61,472 women were used in this analysis. The dataset consisted of 463 total cancers of which 157 were advance stage. Comparing clinical density to DL derived density resulted in a Kappa-score of 0.53.

Models using clinical density and DL density resulted in AUC of 0.57 (95% CI: 0.49, 0.65) and 0.56 (95% CI: 0.50, 0.65), respectively while image only models resulted in an AUC of 0.63 (95% CI: 0.58, 0.69). Combining imaging predictions with clinical density resulted in an AUC of 0.69 (95% CI: 0.62, 0.73) and combining imaging predictions with DL density resulted in an AUC of 0.67 (95% CI: 0.62, 0.72) (Figure).

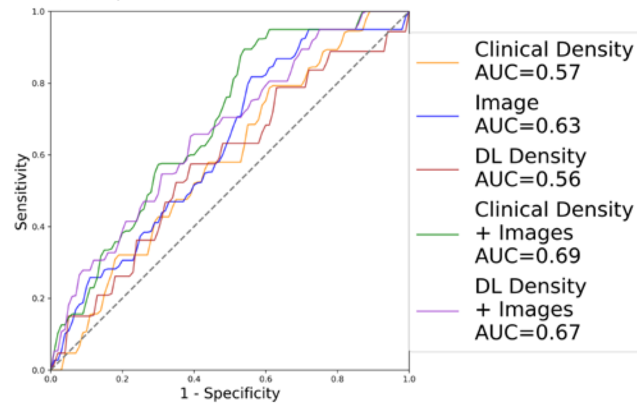

Figure Receiver operating characteristic curve for all logistic models.

CONCLUSION:

Imaging provides signals of advanced stage breast cancer risk that are independent of breast density.

What is the key finding new since 2019?

We have found imaging signals beyond density related to advanced breast cancer which was not known in 2019.

How does this finding impact screening strategies for women?

Women found to be at higher advance stage cancer risk may consider additional or more frequent screening.

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2. Kerlikowske K, Chen S, Golmakani MK, Sprague BL, Tice JA, Tosteson ANA, Rauscher GH, Henderson LM, Buist DSM, Lee JM, Gard CC, Miglioretti DL. Cumulative Advanced Breast Cancer Risk Prediction Model Developed in a Screening Mammography Population. JNCI: Journal of the National Cancer Institute. 2022;114(5):676-85. doi: 10.1093/jnci/djac008.

ARTIFICAL INTELLIGENCE PREDICTS MAMMOGRAPHIC BREAST DENSITY FROM CLINICAL BREAST ULTRASOUND IMAGES

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INTRODUCTION:

Advanced stage breast cancer rates are considerably higher in Hawai'i (15%) and the USAPI (50%) than in the continental US (9%). Efforts to curb advanced stage cancer rates are limited by either lack of access to screening mammography or low participation. Breast density is an important risk factor for advanced staging but is typically estimated from mammography. Screening breast ultrasound (BUS) can be an alternative when mammography is unavailable.

OBJECTIVES:

The purpose of this study is to explore AI-enabled estimation of mammographic density based solely on clinical BUS imaging.

METHODS:

From over 100,000 women participating in the Hawai'i and Pacific Islands Mammography Registry (NIH R01CA263491 and U54CA143728), we selected women with negative screening mammography and BUS visits within 1 year of each other. Cases were defined as women who developed breast cancer within 10 years. Controls were matched to cases on birth year and BUS machine. BI-RADS breast density was estimated from mammograms using a published deep learning model[1]. Breast density was estimated from BUS using three approaches: linear (logistic regression) analysis of binned gray-levels[2] (LogReg method), non-linear (neural network) analysis of binned gray-levels (MLP), and an end-to-end convolutional neural network (CNN). Patients were split into a training set (60%), a tuning/validation set (20%), and a held-out test set (20%). The ability of the models to classify patients into the density categories was compared by measuring the one-vs-rest area under the receiver operator characteristic (AUROC) on the test set.

RESULTS:

We found that 13,263 patients had negative (BI-RADS 1/2) imaging. We excluded 4,468 which did not have a recent density record or mammogram. Our final dataset consisted of 382 case-control sets (1:10) with 101,546 clinical BUS scans and 4,202 full-field digital mammograms. CNN outperformed LogReg and MLP for identifying all four breast density categories. The performance difference is especially significant in the fatty (A) category (AUROCs of 0.53, 0.54, and 0.71 for LogReg, MLP, and CNN, respectively). **Table 1** provides AUROC values computed on one-hot encoded deep-learning derived labels[1]. 95% confidence intervals were computed using DeLong's method[3].

Table 1: AUROC (95% C.I.) of the BI-RADS Breast Density Categories

	LogReg	MLP	CNN
A	0.53 (0.50, 0.57)	0.54 (0.50, 0.57)	0.71 (0.68, 0.74)
B	0.59 (0.58, 0.59)	0.64 (0.63, 0.64)	0.66 (0.65, 0.67)
C	0.57 (0.56, 0.57)	0.62 (0.61, 0.63)	0.65 (0.64, 0.65)
D	0.70 (0.68, 0.72)	0.74 (0.71, 0.76)	0.75 (0.73, 0.77)

CONCLUSION:

High risk (high breast density), as well as low risk (low breast density) classifications are possible from clinical BUS images. A deep learning convolutional neural network outperformed both methods using predefined gray-level features.

What is the key finding new since 2019?

We have found that imaging signals in clinical breast ultrasound are predictive of mammographic density through deep learning. This is a novel finding.

How does this finding impact screening strategies for women?

Women living in areas where mammography is unavailable may receive accurate breast cancer risk measures from breast ultrasound alone.

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1. Wu N, Geras KJ, Shen Y, et al. Breast Density Classification with Deep Convolutional Neural Networks. IEEE; 2018:
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3. Sun, X. and W. Xu, Fast Implementation of DeLong's Algorithm for Comparing the Areas Under Correlated Receiver Operating Characteristic Curves. IEEE signal processing letters, 2014. 21(11): p. 1389-1393.

PREDICTING LESION MASKING RISK IN MAMMOGRAMS IN THE DUTCH NATIONAL BREAST CANCER SCREENING PROGRAM

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INTRODUCTION:

In the Netherlands, all women between 50 and 75 years of age are invited biennially for mammographic screening. Although the cancer detection rate is high, at 6.9 per 1,000,[1] there are still 2.2 interval cancers per 1,000 women screened. These cancers include true interval cancers, and those present at screening but missed, due to being outside of the field of view, or masked by superposition by fibroglandular tissue. Predicting the lesion masking risk could flag these cases for radiologists to pay extra attention to during reading or recommend for supplemental imaging, such as MRI or breast CT to be performed.

Previously, a method has been developed to predict lesion masking risk in screening mammograms.[2] Prediction is based on radiomics features of density and detectability maps generated by a model observer, as well as clinical factors such as age and body-mass index (BMI). It has been validated using contralateral mammograms of screen detected (SD) cancers, in which the lesion was not masked, and non-screen- detected (NSD) ones, in which the lesion was most likely masked. However, the model was only tested on a limited dataset of 147 SDs and 67 NSDs.

OBJECTIVES:

The objective of this study is to test if this model is also applicable to the Dutch Breast Cancer Screening Program, with 2-year screening intervals and double reading as opposed to 1-year intervals and single reading in the original dataset.

METHODS:

This model was tested on a dataset of retrospectively collected digital screening mammograms acquired at the Preventicon screening centre located in Utrecht, The Netherlands, between 2003 and 2018. In total, 473 cases with unilateral SDs were included. Furthermore, the last screening cases before 153 unilateral NSDs were included, with maximum of 24 months between screening and diagnosis.

The model was applied to the contralateral images of all 626 cases and predicted lesion masking risk was averaged over the views for each case. Contralateral images were used to eliminate the influence of the lesion. A Receiver Operator Characteristics (ROC) analysis was performed for the discriminative property of the lesion masking score for SD and NSD representing low and high masking risk respectively.

RESULTS:

Figure 1 shows the ROC curve of the model to discriminate between contralateral images of SDs an NSDs. The mean AUC was 0.65 (95%CI 0.60 – 0.69).

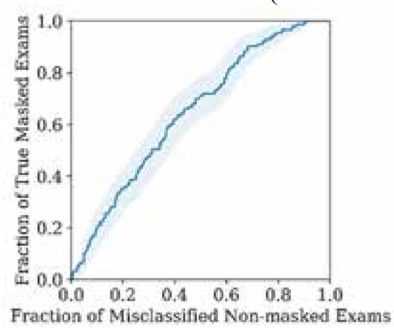

Figure 1. ROC curve of the model in discriminating between SD (low masking risk) and NSD (high masking risk). The shaded region represents the 95% CI.

CONCLUSION:

The model was able to predict lesion masking in the Dutch screening cohort with a comparable AUC to the cohort of the original paper (0.75 95%CI 0.68 – 0.82). Further analysis is necessary to evaluate if the same features drive prediction in both cohorts.

What is the key finding new since 2019?

The prediction of risk of lesion masking is robust across different screening and reading regimens.

How does this finding impact screening strategies for women?

Predicting lesion masking risk in mammograms could aid in reading strategy or the referral for supplemental screening strategies.

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ADVANCING EVIDENCE OF THE ASSOCIATIONS BETWEEN SPECIFIC BENIGN BREAST DIAGNOSES AND FUTURE BREAST CANCER RISK

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[1]University of California at Davis; [2]University of California, San Francisco; [3]University of Vermont

INTRODUCTION:

Benign breast disease (BBD) is a common breast biopsy finding and encompasses a diverse spectrum of diagnoses. Women with certain BBD diagnoses are known to have a high risk for development of invasive breast cancer, with risk varying by degree of histological abnormality with cancerous-like features within the benign lesion. The risk of cancer associated with many specific BBD diagnoses and their joint associations with breast density have not been extensively studied.

OBJECTIVES:

We estimate the future risk of invasive breast cancer associated with specific BBD diagnoses typically combined into two broad categories of non-proliferative lesions (NPL) and proliferative lesions without atypia (PWoA), and to identify clusters of specific diagnoses with similar risk. Further, we evaluate whether these associations differ by breast density categories or by the co-occurrence of certain pathologic descriptors such as calcifications or inflammation.

METHODS:

We included 711,802 women ages 35 to 79 years who underwent 2,606,759 screening or diagnostic mammogram in the Breast Cancer Surveillance Consortium from 1996 to 2020 with no history of breast cancer. We grouped specific pathological terms used to describe the same BBD diagnoses and descriptors. We fit the Cox proportional hazards model to estimate hazard ratios (HR) associated with each combination of benign breast diagnoses, calcification status, and breast density. We then identified specific BBD diagnoses with sufficient sample sizes and used classification trees to group combinations of BBD diagnoses, breast density, age groups, and descriptors with similar magnitudes of associations with 5-year risk of invasive breast cancer.

Table: Breast cancer risk associated with BBD cross-classified with breast density and presence of calcs

Benign breast disease		BI-RADS breast density, HR (95% CI)			
		Almost entirely fat	Scattered fibroglandular densities	Hetergenously dense	Extremely dense
NPL	-calc	0.54 (0.4, 0.73) P<0.001	1.0 (reference)	1.33 (1.19, 1.5) P<0.001	1.45 (1.22, 1.72) P<0.001
	+calc	0.91 (0.56, 1.48) P = 0.7055	1.0 (0.81, 1.24) P = 0.9707	1.45 (1.22, 1.73) P<0.001	1.66 (1.2, 2.28) P = 0.002
PWoA	-calc	0.55 (0.27, 1.14) P = 0.1092	1.18 (0.96, 1.46) P = 0.1187	1.52 (1.26, 1.83) P<0.001	1.66 (1.14, 2.42) P = 0.0078
	+calc	1.03 (0.52, 2.02) P = 0.9372	1.3 (1.02, 1.66) P = 0.0324	2.04 (1.69, 2.46) P<0.001	1.75 (1.17, 2.6) P = 0.006

RESULTS:

Risk of breast cancer increased with breast density and the presence of calcifications. Women with PWoA BBD diagnosis with calcifications and high breast density were at highest risk for future breast cancer (HR = 2.04; 95% CI: 1.69 to 2.46; P<0.001) (**Table**). The 0.04% of women with very high invasive breast cancer risk (5-year risk>4%) were age 60-69 years with heterogeneously or extremely dense breasts and BBD diagnoses papillomas, usual ductal hyperplasia, radial scar, or columnar cell hyperplasia. The 1% of women with high invasive breast cancer risk (5-year risk>2.49%) were age >50 years with heterogeneously or extremely dense breasts or scattered fibroglandular densities and BBD diagnoses mentioned previously, as well as NPL BBD diagnoses such as fibrocystic changes, adenosis, fibroadenomatoid hyperplasia, or fibroadenoma. The 89% of women with low-average risk (0-1.66%) were age <60 years with scattered fibroglandular densities and any NPL BBD diagnosis, or age<50 years with any PWoA BBD diagnosis. Women with almost entirely fat breast density were at low-average risk, regardless of age or BBD diagnosis.

CONCLUSION:

Women with dense breasts and specific BBD diagnoses identified from the lower risk categories of BBD are at high risk of breast cancer. Women with fatty breasts are at low risk of breast cancer regardless of NPL or PWoA diagnosis.

What is the key finding new since 2019?

Specific BBD diagnoses in combination with breast density and presence of calcifications can more accurately identify groups of women at higher or lower risk of breast cancer than broad BBD categories.

How does this finding impact screening strategies for women?

This knowledge can inform subgroups of women most likely to benefit from primary prevention or other prevention efforts.

INTERVAL CANCER PREDICTORS BEYOND A, B, C, D

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INTRODUCTION:

The association between mammography screening performance and breast density is well established, with lower sensitivity and higher interval cancer (IC) rates for women with dense breasts [1,2]. This differential performance can partly be explained by a ‘masking’ effect of fibroglandular tissue. To mitigate this effect, supplemental screening can be offered on the basis of BI-RADS “c” and/or “d” density assessment. In the absence of supplemental screening, consideration is being given to the use of Computer Aided Detection (CAD) algorithms based on Artificial Intelligence (AI) [3]. But masking prediction is the subject of active research [4]. And an understanding of image factors related to the potential lesion conspicuity is especially important in the context of AI use to help explain interpretation performance and to estimate finding uncertainty.

OBJECTIVES:

We aimed to identify image-based predictors of IC relative to screen-detected cancer (SDC).

METHODS:

We retrospectively studied 964 screening mammograms with SDC, and prior round images from 318 IC from the OPTIMAM database [5]. These were matched 3:1 on age, Volpara Density Grade, clinic, and compression paddle to minimize density and positioning confounders. Volpara Imaging Software (v3.4) was used for volumetric breast density (VBD), compression and breast positioning analysis. Other image evaluation included measurement of GLCM features and the power spectrum, as summarized by the anatomical noise parameter, β [4]. Thresholding of Volpara™ Density Maps, at pixel-level 10% VBD with dilation to define continuous regions, was used to select corresponding image regions for β analysis. Univariate and multivariate analysis was performed on aggregated parameters from the affected breast to determine candidate predictors. Predictors were selected using the Akaike information criterion from logistic regression to classify as SDC or IDC.

RESULTS:

Small, but significant differences were found between median SDC and IC compression pressures (8.4 vs 7.8 kPa), and β (2.73 vs 2.77). The β difference was only statistically significant when it had been measured in targeted image regions located by Volpara Density Map thresholding. These parameters were used in multivariate modelling, with pressure defined in three categories: as low (<7Kpa), target (7-15 kPa), and high (>15 kPa).

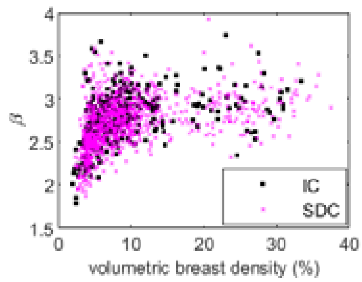

Figure 1. The power spectrum exponent, β, measured from prior IC and incident SDC mammograms as a function of image-level %VBD. Correlation of β with VBD is moderate at 0.40 (SDC) to 0.41 (IC).

Table 1: Odds ratios of SDC vs IC model coefficients.

Predictor	Odds Ratio (95% CI)	P value
intercept	10.90 (3.40-34.97)	5.9E-5
Target:Low pressure	1.45 (1.10-1.91)	0.0075
High:Low pressure	2.15 (1.01-4.56)	0.0456
β	0.57 (0.37-0.87)	0.0090

CONCLUSION:

Our findings suggest that additional factors beyond breast composition can be used to describe the odds of SDC relative to IC. Future work is required to optimize β measurement, and to understand if these additional measures can be computed reliably across all image types and populations.

What is the key finding new since 2019?

The power spectrum exponent, β, measured in dense regions of a mammogram is shown to be an independent predictor of SDC vs IC. Compression pressure findings reinforce previous work showing an influence on mammography performance [6,7].

How does this finding impact screening strategies for women?

Specific attention should be given to achieve good compression pressure. Measures to explain AI performance could incorporate these predictors.

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AN ANALYSIS OF HIGH PERFORMING INSTAGRAM POSTS TARGETED AT CANCER SURVIVORS

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INTRODUCTION:

Breast Cancer Hawaii is a grassroots nonprofit with a mission to connect Hawaii's breast cancer patients, survivors, thrivers, and their families with relevant resources and meaningful support. Our programs and services are designed and managed by cancer survivors based on feedback received from the local cancer community. Such programs include Keiki Care Kits - monthly activity kits sent to children with a parent in cancer treatment, CARE Closet (Community Access to Reusable Equipment) - delivering new and gently used support equipment such as wigs, wedge pillows, and reference books to patients in treatment, and Outdoor Enthusiasts Club - low-impact outdoor activities for cancer survivors.

We also communicate information of interest to local cancer survivors via a number of grassroots channels including in-person resource fairs, electronic newsletter, emails through our network of healthcare providers, and social media. Based on the behavior patterns of our most engaged clients, as well as the platform's capability to capture and track historical engagement metrics, we have increasingly invested efforts into Instagram as our tool of choice for social media.

OBJECTIVES:

The objective of this analysis was to determine if there were factors that influenced the performance of Instagram posts.

METHODS:

Our highest performing Instagram posts from the period May 2021 - May 2023 were assessed for engagement. Each post was analyzed and categorized by the top factor that drove engagement: hashtags, reel, paid ad, and relevance. Engagement performance was measured by the number of times each post was on screen (impressions) and the number of followers and non-followers who have seen each post (reach).

RESULTS:

Our top-performing post had a reach of 1,969 accounts and 68.2% of impressions were driven from hashtags. In comparison, our average 2022 Instagram post had 5.8% of its impressions driven from hashtags. Reach for our top reel was a total of 1,700 accounts consisting of 682 followers and 1,018 non-followers. Reach for a non-reel post with similar content was a total of 850 accounts consisting of 650 followers and 200 non-followers. Our top paid ad reached a total of 1,522 accounts, whereas our 12-month reach average was 486 accounts. Our 4th top-performing post was made during Breast Cancer Awareness month and had a reach of 1,175 accounts, consisting of 757 followers and 418 non-followers.

CONCLUSION:

Reach grows through non-followers. Hashtag-driven posts increase impressions from hashtags, reels compared to non-reels increase the number of accounts reached especially to non-followers, and effectively targeted ads all can be useful in reaching a broader audience. These strategies are relatively easy to implement and can be a tool for disseminating health information to the general community.

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THE HAWAII AND PACIFIC ISLANDS MAMMOGRAPHY REGISTRY

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INTRODUCTION:

Despite recent advances in early detection and treatment, breast cancer remains a major cause of morbidity and mortality among women in the U.S. Notable racial/ethnic differences in incidence and survival have been described[1]. For example, Native Hawaiian women have the highest breast cancer incidence in Hawaii despite their favorable reproductive patterns. Japanese American women now experience the same breast cancer risk as non-Hispanic White women, although the incidence in Japan is still lower. Also, percent mammographic areal density is high in Japanese American women due to their smaller breast size, but their dense volume is lower. Further, the percentage of breast cancers that are advanced are considerably higher in Asian American Women in Hawaii and the Pacific compared to the US mainland, 15% versus 9%.

We present the Hawaii and Pacific Islands Mammography Registry (HIPIMR) which contains over 100,000 unique women undergoing breast imaging in the state of Hawaii. Included are demographic, clinical, and risk factor information, and cancer outcomes obtained through linkage with the Hawaii Tumor Registry (HTR) and Hawaii State Department of Health and Vital Records (HSDHVR).

OBJECTIVES:

The main goals of the registry are to: 1.) Identify next-generation breast imaging characteristics and their association with breast cancer in women of various ages and ethnicities, 2.) Examine clinical risk factors in women undergoing breast cancer screening in disadvantaged and underrepresented communities in Hawaii and the Pacific Islands, 3.) Improve the accuracy and accessibility of breast cancer screening through quality control, alternative technology, and artificial intelligence.

METHODS:

The HIPIMR is currently supporting various research efforts:

1.) Artificial intelligence predicts mammographic breast density from clinical breast ultrasound images
2.) Image-Based Models for Predicting Advanced Breast Cancer Risk
3.) Makawalu Study: Breast cancer screening in the Pacific using Portable Ultrasound
4.) Breast Health Questionnaire Standardization

RESULTS:

Table 1: General demographic information and counts of the current HIPIMR database.

	HIPIMR
ELIGIBLE YEARS	2009-2023
TOTAL PAST IMAGING VISITS, N	470718
TOTAL UNIQUE WOMEN	104904
TOTAL NUMBER OF DICOM IMAGES	
MEAN AGE (SD)	57.64 (12.56)
RACE/ETHNICITY %	
HISPANIC (ALL)	0.9
WHITE, NON-HISPANIC	24.6
ASIAN	56.5
BLACK, NON-HISPANIC	1.2
NATIVE HAWAIIAN/PACIFIC ISLANDER	16.5
AMERICAN INDIAN/ALASKA NATIVE	0.4
ESTIMATED NEW PARTICIPANTS EACH YEAR (80% RETENTION)	7235
TOTAL OF WOMEN BY IMAGING MODALITY	
MAMMOGRAPHY	78139
ULTRASOUND	30870
MAGNETIC RESONANCE IMAGING	1879
DIGITAL TOMOSYNTHESIS	33792
TOTAL NUMBER OF MALIGNANCES	5042

CONCLUSION:

The HIPIMR is an invaluable resource for the people of Hawaii, and allows researchers to anwser ethnic specific questions regarding breast cancer risk disparities.

What is the key finding new since 2019?

The HIPIMR has grown significantly since 2019 which has greatly expanded the types of research questions and projects relating to breast cancer risk for women in Hawaii.

How does this finding impact screening strategies for women?

The HIPIMR enables researchers to anwser questions about breast cancer screening and risk that are specifically tailored for the unique ethnic profile of the women of Hawaii in comparison to the continental United States.

Course Roster

1.	Abubakar, Mustapha	National Cancer Institute, NIH
2.	Acerbi, Irene	Exai Bio Inc.
3.	Akana, Anela	University of Hawaii Cancer Center
4.	Arasu, Vignesh	Kaiser Permanente, Northern California Division of Research
5.	Austin, Jessica	Mayo Clinic Arizona
6.	Baptiste, Deana	American Cancer Society
7.	Batchelder, Kendra	University of Maine
8.	Bennett, Jonathan	University of Hawaii Cancer Center
9.	Bertrand, Kimberly	Slone Epidemiology Center at Boston University
10.	Binder, Alexandra	University of Hawaii Cancer Center
11.	Bowen, Aimee	University of Hawaii Cancer Center
12.	Bunnell, Arianna	University of Hawaii
13.	Cataldi, Devon	University Of Hawaii At Manoa
14.	Chandler, Kylie	Volpara Health
15.	Chin, Cheryl	Exai Bio
16.	Colditz, Graham	Washington University School of Medicine
17.	Cummings, Steven	San Francisco Coordinating Center, California Pacific Medical Center Research Institute
18.	Duluk, Corinne	Delphinus Medical Technologies
19.	Duric, Neb	University of Rochester
20.	Eriksson, Mikael	Karolinska Institutet
21.	Faatonu, Sally	American Samoa Department of Health
22.	Fan, Shaoqi	National Cancer Institute
23.	Funakoshi, Jena	University of Hawaii Cancer Center
24.	Gabrielson, Marike	Department of Medical Epidemiology and Biostatistics, Karolinska Institutet
25.	Gastounioti, Aimilia	Washington University School of Medicine in St. Louis
26.	Getz, Kayla	Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine in St. Louis
27.	Gierach, Gretchen	National Cancer Institute/Integrative Tumor Epidemiology Branch
28.	Gunn, Christine	The Dartmouth Institute for Health Policy and Clinical Practice
29.	Hall, Per	Karolinska institutet
30.	Hamilton, Joshua	University of Maine
31.	Harris, Alexandra	National Cancer Institute
32.	Harris, Holly	Fred Hutch Cancer Center
33.	Harrison, Tabitha	University of Washington
34.	Hayashi, Joanne	Breast Cancer Hawaii
35.	Heckman-Stoddard, Brandy	National Cancer Institute/Division of Cancer Prevention
36.	Highnam, Ralph	Volpara Health
37.	Hill, Melissa	Volpara Health
38.	Hirsch, Lukas	City College of New York
39.	Ho, (Yuki) Weang Kee	University of Nottingham
40.	Horng, Hannah	University of Pennsylvania
41.	Hughes, Elisha	Myriad Genetics

42.	Irish, Jennifer	Myriad Genetics
43.	JAYASEKERA, Jinani	NIN/NIMHD
44.	Jenkins-Lord, Brittany	National Cancer Institute
45.	Jiang, Shu	Washington University School of Medicine
46.	Kazemi, Leila	University of Hawaii
47.	Kehm, Rebecca	Columbia University
48.	Kelly, Nisa	University of Hawaii Cancer Center
49.	Kerlikowske, Karla	UCSF
50.	Khalil, Andre	University of Maine
51.	Khan, Seema	Northwestern University
52.	KIM, WON HWA	Kyungpook National University Hospital
53.	Kontos, Despina	University of Pennsylvania
54.	Kuioka, Elizabeth	UH Cancer Center
55.	LANGE, JANE	OREGON HEALTH AND SCIENCES UNIVERSITY
56.	Lauritzen, Andreas	University of Copenhagen
57.	Lee, Juhun	Univ of Pittsburgh
58.	Lee, Eunjung	University of Southern California
59.	Lindstroem, Sara	University of Washington
60.	Maidment, Andrew	University of Pennsylvania
61.	Maluo, Joni	Myriad Genetics
62.	Maskarinec, Gertraud	University of Hawaii Cancer Center
63.	Michels, Karin	University Medical Center Freiburg
64.	Miglioretti, Diana	University of California, Davis
65.	Moon, Woo Kyung	Department of Radiology, Seoul National University Hospital
66.	Mullooly, Maeve	RCSI University of Medicine and Health Sciences
67.	Ng, Susan	University of Pennsylvania
68.	Nguyen, Alex	University of Pennsylvania
69.	Nielsen, Mads	University of Copenhagen
70.	OHUCHI, NORIAKI	Tohoku University
71.	Palmer, Julie	Boston University
72.	Park, Hannah Lui	UC Irvine
73.	Pederson, Holly	Cleveland Clinic
74.	Pereira, Ana	Institute of Nutrition and Food Technology, University of Chile
75.	Plotkin, Daneil	Delphinus Medical Technologies
76.	Ramin, Cody	Cedars-Sinai Medical Center
77.	Ryan, Austin	MagView
78.	Salim, Mattie	Karolinska institute
79.	Sattayapiwat, Olivia	University of California, Davis
80.	Sechopoulos, Ioannis	Radboud University Medical Center
81.	Shepherd, John	University of Hawaii Cancer Center
82.	Snow, Michelle	White River Health

83.	Stone, Jennifer	University of Western Australia
84.	Strand, Fredrik	Karolinska Institutet
85.	Tamimi, Rulla	Weill Cornell Medicine
86.	Tehranifar, Parisa	Columbia University
87.	Terry, Mary Beth	Columbia University
88.	Tice, Jeff	UCSF
89.	Tingberg, Anders	Skane University Hospital
90.	Tolentino, Katrina	Breast Cancer Hawaii
91.	Toriola, Adetunji	Washington University in St. Louis
92.	Trentham-Dietz, Amy	University of Wisconsin-Madison
93.	Vachon, Celine	Mayo Clinic
94.	Vaimauga, Sasagi	American Samoa Department of Health
95.	Valdez, Dustin	University of Hawaii Cancer Center
96.	Vedantham, Srinivasan	University of Arizona
97.	Verboom, Sarah	Radboud University Medical Center
98.	Warner, Erica	Massachusetts General Hospital
99.	Watt, Gordon	Memorial Sloan Kettering Cancer Center
100.	Willis, Jasmay	American Samoa Department of Health BCCP
101.	Wong, Michael	University of Hawaii Cancer Center
102.	Yala, Adam	UC Berkeley and UCSF
103.	Ye, Zhoufeng	University Of Melbourne

—
Hopefully, we've successfully concluded the workshop without an incident like the Hotel Kabuki fire at the 7th IBDW *San Francisco* (2015)

Mahalo for 10 Memorable Workshops!










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Group photo at 8th IBDW
San Francisco (2017)







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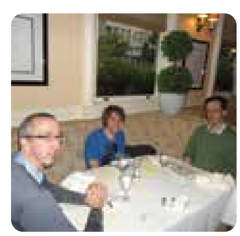
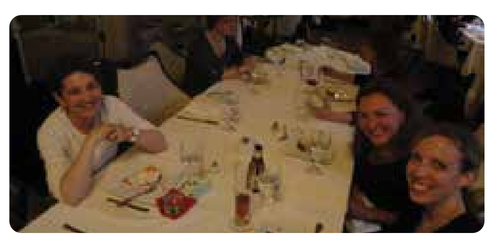
Thank you Alice for your work in planning the San Francisco workshops!

Alice LaRocca at the 7th IBDW in 2015.







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